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A NEW CONCEPT OF THE ETIOLOGY OF MEGALOURETERS*

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BOSTON

THE association of megalobladder and megaloureters with megacolon has been reported.[1-3] Twenty-two of our patients with Hirschsprung's disease were studied with cystometrograms; in 12 patients the bladder capacity was considerably above normal. In 7 of these the changes were pronounced, with absence of emptying contractions in response to filling increments. Maximum distention of the bladder produced an urge to void and emptying seemed to take place because of increased intra-abdominal pressure following strong voluntary contractions of the abdominal musculature. In addition to these bladder abnormalities, 3 patients with bilateral megaloureters and 1 with a unilateral megaloureter were treated in our series of 76 patients operated on for congenital megacolon.

The present conception of the pathology in Hirschsprung's disease is an absence of peristalsis in the rectosigmoid. The resultant functional obstruction in this region produces dilatation and hypertrophy of the adjacent proximal colon.[4-7] The rectosigmoid in this disease contains no Auerbach's-plexus ganglion cells. As these ganglia are a part of the parasympathetic innervation from the pelvic nerves, the congenital absence of mesenteric ganglion cells in the rectosigmoid in Hirschsprung's disease probably represents a maldeveloped pelvic parasympathetic system. This makes it reasonable to assume that some patients with Hirschsprung's disease may also have faulty innervation of the bladder musculature, which is normally supplied by this portion of the autonomic system. One could postulate further that there should be a group of patients with the bladder defect only; we believe these are the patients with megaloureters.

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A test of this hypothesis would be the demonstration of an abnormality of the parasympathetic system in the bladder.

PATHOLOGY

The material for this study comprised 7 bladders from infants and children who at autopsy had shown the clinical manifestations and characteristic findings of megalobladder and megaloureter. Also studied were 1 large segment and 4 single blocks from the posterior wall of the bladders of 5 living children showing the same anomaly. As controls, healthy bladders from 9 infants and children and a large section taken at autopsy from the posterior wall of a healthy adult bladder were examined. In the autopsied cases, the blocks were generally 0.5 cm. in thickness and 1 section from each block was cut and stained. The blocks were taken from the midline posteriorly, extending from the urethra to the fundus. Blocks were than taken transversely from the midline anteriorly to the lateral extremity of the posterior section and extending from the urethra to the fundus. These sections then encompassed one half of each bladder and included the mucosa, muscularis and adventitia. The number of blocks taken from each bladder varied from 10 to 35, and there was considerable range in the size of the blocks.

Tissues were fixed in formalin, embedded in paraffin and stained by routine methods. All elements of the bladder were examined, particular attention being focused on the ganglia, nerve cells and nerve fibers. The aim was to survey and estimate the number, character and distribution of ganglion cells in all regions of the bladder. For clarity in this report the term "test bladder" will be used to indicate one showing megalobladder associated with megaloureters, and "control bladder" will be used to designate the normals.

This study showed a remarkable uniformity in the pattern of distribution of both ganglia and nerve cells throughout the control series. These were almost exclusively located in the adventitia of the bladder, and the greatest concentration lay near

the entrance of the ureter into the bladder. Ganglia were also concentrated around the seminal vesicles in the male and near the vaginal septum in the female. These areas contained multiple ganglia of varying size and nerve cells of two types, one being round and the other scalloped in outline. In addition, satellite cells and cells of the neurilemma were found in abundance in ganglia in small groups and singly within the substance of nerve bundles. The nerves and nerve cells were concentrated in the adventitia in the lateral portions of the trigone, and the number diminished as one reached the midline anteriorly and posteriorly and as one explored from the level of the ureters toward the fundus and toward the urethra. From these areas nerves and small nests of nerve cells, usually following the course of larger vessels, could be traced from the adventitia into the deeper zone of the muscularis. In rare instances ganglion cells were seen singly, in pairs and in small clusters in the superficial muscularis and submucosa. The nerves, almost exclusively nonmyelinated, were found in all layers of the bladder.

The larger the block, the greater the chance of finding either ganglia or nerve cells; transverse sections revealed many more nerve cells than did blocks taken sagittally. These two points may seem irrelevant, but in normal bladders small sections taken at random, — and even large blocks taken from the midline anteriorly, posteriorly or through the fundus, — may be entirely free of nerve cells. This last point was shown clearly in one of the control bladders in which no ganglion cells were found in a continuous series of sagittal sections taken from the midline of the posterior wall.

In six of the seven test bladders there was an absolute diminution in the number and size of the ganglia, in the number and variety of nerve cells and in the number of nerve bundles. However, the distribution of nerve cells in the test bladders was generally the same as that in the control series. It is important to stress that some ganglion cells were found in each test case. In one of the test bladders a section contained only one small nest of ganglion cells bordering one ureter, and the rest contained none. Another finding common to most of the test bladders was a variable degree of inflammatory edema. Each of the test bladders showed more or less dilatation and hypertrophy of the muscularis.

Two of the bladders from the test group will be described in detail.

A-50-34 (*B.F.H.*). This bladder was from a child with megalobladder, bilateral megaloureter and moderately severe microgyria of the brain. Thirty-one small blocks were taken from the bladder and the first portion of the urethra. Of the 31 blocks, ganglion cells were found in only 9. No ganglion cells were found in 5 serial transverse blocks from the lowermost portion of the bladder and the first portion of the urethra. In 13 blocks taken from the midline area of the posterior wall, ganglion cells were found in 2; only 1 cell was found in each of these 2 sections. A total of 7 blocks was cut from the right and left of the midline posteriorly, corresponding roughly to the posterolateral margin of the bladder. In 6 of these ganglion cells were demonstrable, but in 1 of the 6 only 1 cell was found; in 3 of the blocks, only 2 ganglion cells were seen; and in the remaining 2 blocks, representing the area adjacent to the lower end of the ureter, only small solitary clusters of cells were seen. The remaining 6 blocks were taken from the anterolateral surface of the bladder bilaterally; in 1 of these sections 2 ganglion cells were found. The total number of ganglion cells counted in all 31 blocks was 43, which is only a small portion of the average number of cells found in the controls. It must be emphasized at this point that actual counts of nerve cells were not made in every case.

A-50-38 (*B.F.H.*). This bladder was from a child showing megalobladder, bilateral megaloureter, megacolon and congenital hydrocephalus. A total of 10 large-to-medium-sized blocks were taken to represent all parts of this bladder, each block including all coats, with abundant adventitia. In this case ganglion cells were found in *all* sections. They were confined to the adventitia and outer layer of muscularis. The greatest concentration was found bilaterally, adjacent to the lower ends of the ureters. In these two areas ganglion cells were moderately abundant, occurring in small clusters and lying within the substance of nerve bundles. In all other areas they occurred sparsely, singly and in groups of 2, 3 and 4. Nerves were present in all sections and in all coats of the bladder. It must be emphasized that although nerve cells were found in all sections the blocks from which these sections were made were larger than in the preceding case, and often only a single cell was found after long search. It was apparent that, as in the case just described, it would have been possible to cut many smaller blocks from this bladder without finding a single ganglion cell. In comparison with the control group, the total number of ganglion cells was far less than normal.

In full cognizance of the defects in a study of this type, which at best is only a sampling of bladders in varying stages of contraction and dilatation from persons showing varying degrees of disturbance in function, every effort was made to treat the control and test bladders as nearly alike as possible. Study of the test bladders demonstrated a diminution of ganglion cells. To evaluate this impression, an attempt was made to see if it would be possible to distinguish the test from the control bladders by a search for ganglion cells without having a key to either the clinical history or autopsy findings. There were 16 cases in all; from this group 6 were selected as showing a definite diminution in the number and size of ganglia and in the actual number of nerve cells. The remaining 10 were classed as having normal nerve-cell counts. Actually, by clinical and autopsy findings there were 7 cases of megalobladder and megaloureter in this group of 16; of these 7 it had been possible to identify 6 by the method outlined above. In retrospect the seventh case, might be regarded, histologically at least, as borderline.

This one case, which we failed to identify by cell count alone, was a typical example of megalobladder and megaloureter, both by clinical signs and symptoms and by autopsy findings. In many sections of this bladder there were no ganglion cells (it will be recalled that sections from a healthy bladder may also show no ganglion cells), but many ganglia, ganglion cells and nerve fibers were found near the lower end of the ureter. When this case was reviewed for the first time, it was classed as an example of megalobladder because of the large number of sections showing no ganglion cells, but on the second examination (still without any clinical information or knowledge of the autopsy findings) it was reclassified as within normal limits. This impression was based on the number of ganglion cells at the ureterovesical junction. Such a case as this is important, as it shows that a diminution in ganglia or cell count may not always go hand in hand with megalobladder. It also suggests the possibility that an anomalous distribution of cells may be a significant factor or that the nerve cells or the nerves themselves may be functionally defective. At least it indicates that on sampling the number of nerve cells may in certain cases of megalobladder fall within the range of normal.

The selection of 6 out of 7 cases of megalobladder by nerve-cell estimation alone, out of a group of 16 bladders, suggests that a diminution in nerve cells may be the anatomic basis for what was considered a primary functional disturbance of the bladder.

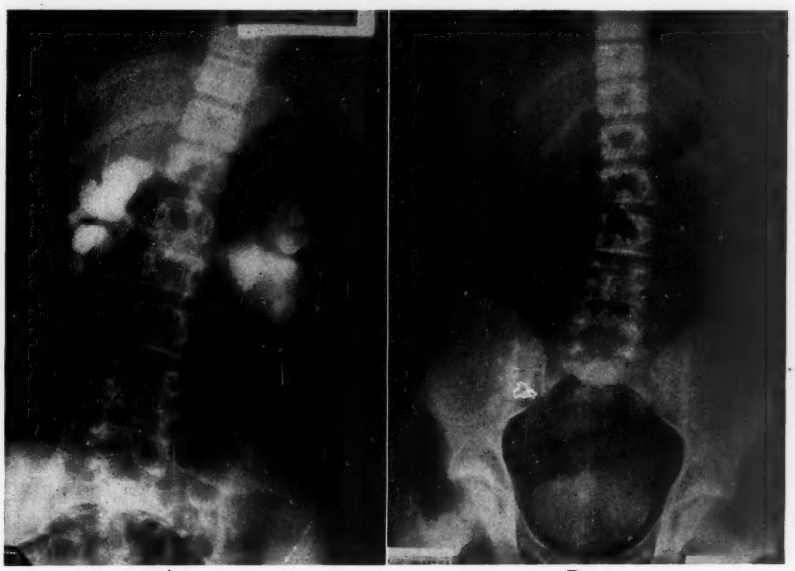
We believe that the following 8 living patients have the same basic lesion as was demonstrated in our autopsy material:

Case Reports

Case 1. A 9-year-old boy was admitted to the hospital with acute urinary retention. He had a long history of infrequent urination. A soft rubber catheter was easily inserted into the bladder, and over 1000 cc. of urine was drained. We expected to find posterior urethral valves as the explanation of the retention. However, a urethrogram, urethroscopic examination and a suprapubic cystotomy with retrograde probing of the urethra revealed no mechanical obstruction. A cystogram showed a huge bladder with no retrograde flow of sodium iodide into the ureters. A retrograde urogram revealed bilateral megaloureters. The patient was treated for 6 months with suprapubic drainage, with remarkable improvement in his general condition. A repeat pyelogram then demonstrated a decrease in the size of the ureters and the bladder. After clamping the suprapubic catheter the patient voided easily. The suprapubic tube was removed at this time and the patient was placed on a schedule of voiding 4 times a day. He was taught to use manual suprapubic pressure to promote complete emptying. Three months later the residual ranged from 10 cc. to 20 cc., and he continued in excellent health. Two years later the intravenous urogram was unchanged and the residual was 10 cc. The general condition of the child was excellent.

Case 2. A 13-year-old girl had a long history of urinary infection and infrequent voiding. Intravenous urograms had revealed some hydronephrosis at 6 years of age but no evidence of obstruction. She had gradually lost weight and was irritable and anemic. Laboratory examination revealed the the nonprotein nitrogen was 56 mg. per 100 cc; the urine contained many white cells. Intravenous urograms, on admission, demonstrated marked hydronephrosis and some suggestion of a block at the ureteropelvic junctions. Retrograde urograms revealed megaloureters. A renal exploration on the right side was performed despite markedly dilated ureters. No mechanical obstruction was present. Bladder studies showed a large, atonic bladder with a residual of 500 cc. and no obstruction in the bladder neck or urethra. A suprapubic punch was performed and suprapubic drainage was instituted for four months. During this period the nonprotein nitrogen became normal; the patient's general condition improved, and she gained 30 lb. After removal of the suprapubic tube, the patient voided 4 times a day, using manual pressure to reduce the residual to a minimum. A repeat intravenous urogram demonstrated a marked improvement in the hydronephrosis (Fig. 1).

After removal of the suprapubic catheter, the residual was 15 cc. This gradually rose to 35 cc. in a few months. During a bout of urinary infection the residual was 125 cc; it fell to 40 cc. after the infection was eliminated. A therapeutic resection of the bladder neck was performed. Two months after this her residual was 35 cc.; a month later it was the same.

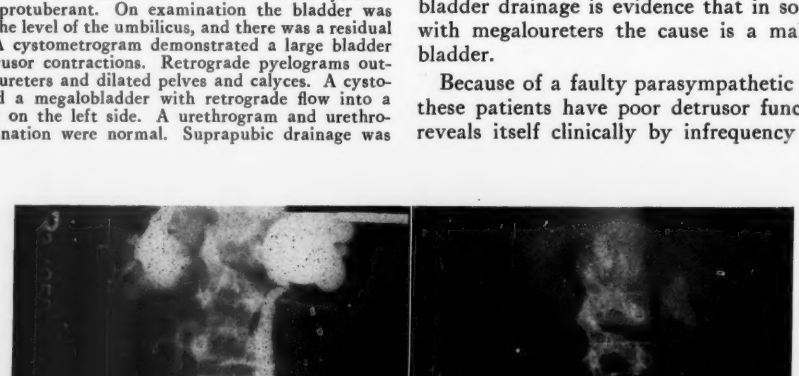


A B

Figure 1. *Intravenous Urogram in Case 2, Taken Before* (A) *and After* (B) *Four Months of Suprapubic Drainage.*

Case 3. An 8-year-old boy was admitted for cryptorchidism. On examination the bladder was found at the level of the umbilicus. Roentgenograms of the abdomen showed anomalies of the lumbar spine. Neurologic examination was negative except for the enlarged bladder. A myelogram was performed; no evidence of disease was found in the cord. This patient had a hypospadias, and catheterization of the bladder was difficult. At cystotomy no obstruction in the bladder outlet or urethra was found. A No. 14 soft-rubber catheter met no obstruction when passed from the bladder through the urethra. A cystogram outlined a megalobladder with retrograde filling of huge bilateral ureters and dilated pelves and calyces. A repeat cystogram, after 8 months of suprapubic drainage, showed a fairly normal-sized bladder, slight reflux on the right side and a marked decrease in the hydroureter and hydronephrosis on the left side (Fig. 2). This patient's tube has recently been removed, and he is doing well.

CASE 4. A 7-year-old boy was hospitalized for urinary-tract infection. He had a long history of infrequent urination. His mother stated that his lower abdomen had always been abnormally protuberant. On examination the bladder was palpable at the level of the umbilicus, and there was a residual of 300 cc. A cystometrogram demonstrated a large bladder without detrusor contractions. Retrograde pyelograms outlined megaloureters and dilated pelves and calyces. A cystogram showed a megalobladder with retrograde flow into a megaloureter on the left side. A urethrogram and urethroscopic examination were normal. Suprapubic drainage was instituted, with considerable improvement in the patient's general health. A repeat cystogram after 4 months of suprapubic drainage revealed a normal bladder with reduction in size of the megaloureter.



A B

FIGURE 2. *Cystograms in Case 3.*

A = before treatment, showing megalobladder and reflux into megaloureters. B = after eight months of suprapubic drainage, showing normal-sized bladder, with slight reflux on the right side. Some reflux is still evident on the left side, but marked reduction in the size of the ureters and pelvis is seen.

Four other patients were treated in the same manner; they have shown favorable responses to suprapubic drainage.

These eight patients had no symptoms of Hirschsprung's disease, and motility studies of the rectosigmoid recorded normal peristalsis. Roentgenograms of the abdomen revealed no dilatation of the colon or fecal impaction. All data on these patients indicate a normal parasympathetic system in the rectosigmoid.

The value of prolonged suprapubic drainage in patients with megaloureters is demonstrated by our patients' good clinical response to this form of treatment. There was remarkable improvement of general health, with impressive gains in weight. Additional evidence of the efficacy of this therapy was the striking decrease in the hydronephrosis and size of the ureters and bladder. This response to bladder drainage is evidence that in some patients with megaloureters the cause is a malfunctioning bladder.

Because of a faulty parasympathetic innervation these patients have poor detrusor function, which reveals itself clinically by infrequency of voiding and incomplete emptying of the bladder. Cystometrograms reveal an absence of emptying contractions and a gradual rise of intravesical pressure; thus, when the bladder is half filled the pressure is 20 to 30 cm. of water, which represents two to three times the normal intravesical pressure. This indicates that for some time between urinations the kidneys secrete in the face of an abnormal intravesical pressure and that this is a large factor in producing megaloureters and hydronephrosis. Furthermore, with a large bladder extending up to the umbilicus, the abdominal-muscle contractions are directly transmitted to the bladder, thus undoubtedly increasing intravesical pressure. This factor does not directly affect to the same degree a normal-sized bladder deep in the pelvis. Another consideration in these cases is the presence of large urinary residuals and the resulting urinary infection. This infection augments the enlargement and the poor function of the upper urinary tract.

The reason for malfunction of the ureters in this disease cannot definitely be given. Our studies of ganglion cells in the ureters permit no conclusions. Normal ureters contain only occasional ganglion cells, and we encountered very few, even in the megaloureters. There is evidence that the parasympathetic system helps to mediate a reflex contraction of the lower ureter during emptying of the bladder. Such a neuromuscular mechanism would be important in preventing reflux of urine from the bladder into the ureter during voiding.[8] A reflex of this type may be impaired in bladders with an abnormal parasympathetic supply such as have been described; this may be a large factor in the formation of megaloureters. Certainly, most patients with megaloureters have free reflux from the bladder.

In the etiology of megaloureters and megalobladder another parasympathetic function in the bladder must be taken into account. The parasympathetic innervation probably plays a role in relaxing the sphincter mechanism in preparation for and during urination.[9] This mechanism may be impaired in bladders with a defective parasympathetic supply, and this defect would contribute to the formation of megalobladder and megaloureters. It is important to re-emphasize that in the cases under discussion there was no demonstrable mechanical obstruction that might account for the dilatation.

Megaloureters are common with long-standing cord bladders, and we believe the fundamental cause is a malfunctioning bladder. In many ways the bladders described above are similar to cord bladders, as has been pointed out by Campbell.[10]

One can only speculate concerning why the advanced forms of megalobladder and megaloureter are not more frequently found in Hirschsprung's disease. It is true that patients with megacolon are subjected throughout their lives to frequent enemas, forcing them regularly to exert strong intra-abdominal pressure, which is probably an important factor in emptying the bladder and in reducing residuals. This may be the reason that these patients suffer relatively little inconvenience from their defective bladders.

After operation patients with Hirschsprung's disease are instructed to void four times a day and to make a great effort to empty their bladders completely. Manual suprapubic pressure is recommended.

An ideal method for correction of megalobladder and megaloureter of this type has not been found. Prolonged drainage is efficient but is inconvenient for the patient and his family. However, it limits activity very little, and the small rubber bag attached to the thigh can easily be emptied, even by four-year-old children (Fig. 3). After four to six months of drainage the bladder function is improved and the patients completely empty their bladders. It is important to teach these children to empty their bladders at least four times a day and to use manual suprapubic pressure to ensure complete emptying. Some patients, however, gradually develop more residual, which will probably again decompensate their bladders. Nevertheless this method of treatment is far superior to any other method presently in use.[11]

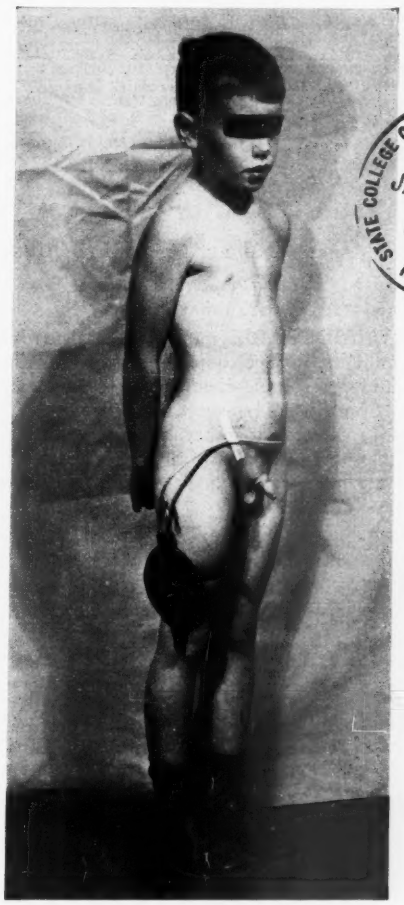


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FIGURE 3. *Photograph of Seven-Year-Old Boy, Showing the Type of Drainage System Used. The bag is conveniently arranged for drainage from the lower end.*

CONCLUSIONS

The diminution of parasympathetic ganglion cells in the bladder may be the fundamental lesion in the megalobladder associated with Hirschsprung's disease.

The bladder in some patients with megaloureters is abnormal in function because of a diminution in parasympathetic ganglion cells.

The megaloureters are the result of this bladder dysfunction.

Clinically prolonged suprapubic bladder drainage results in decrease in the size of the megaloureters and in general improvement of the patient.

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DEATHS FROM POISONING*

Massachusetts, 1938–1948

Merrill Moore, M.D.,† Leo Alexander, M.D.,‡ and Johannes Ipsen, Jr., M.D.§

BOSTON

A CONSIDERABLE number of deaths are caused annually by poisoning — absorption of gaseous, liquid or soluble chemicals. The mortality of deaths from poisoning exceeds, at present, that of all infectious diseases together, with the exception of tuberculosis, and is clearly a public-health problem that warrants attention. The heterogeneous group of causes that is included in official reporting as "poisoning" comprises many phases of medical, epidemiologic and sociologic concern, and the information to be had from an analysis of deaths from poisoning is related to such more specific problems of public health, toxicology and medicine as suicide, accidents, alcoholism and drug addiction.

Ten years ago Alexander, Moore and Leary[1] reviewed deaths from poisoning in Massachusetts from 1928 to 1937. The analysis was based on the original case reports from the medical examiner, which are kept in the Archives Division of the office of the Secretary of State. A scrutiny of these yielded more complete information, particularly pertaining to alcoholism, than the annual report of the medical examiner, to be found in Annual Reports on the Vital Statistics of Massachusetts.[2] Also, subgroupings by specific poisonous substances could be obtained by this direct method, whereas the annual report either has too general classifications or has changed subgroupings during the period of study.

The same basic material, for the period 1938–1948, is analyzed in this paper. The categories and the tabular matter are comparable to those of the

Table 1. *Deaths Certified by Medical Examiners, According to Nature of Poison: Massachusetts, 1938–1948.*

Year	No. of Reports	No. of Poisonings	Alcohol	Carbon Monoxide	
				Illuminating Gas	Other
1938	10,238	815	454	133	100
1939	10,353	814	421	144	98
1940	10,598	747	351	145	91
1941	10,552	741	378	141	63
1942	10,970	724	428	134	39
1943	11,465	725	388	165	42
1944	10,378	627	287	170	47
1945	10,971	705	324	172	55
1946	10,926	697	317	151	68
1947	11,621	700	330	153	57
1948	11,766	673	314	140	56
Totals	119,838	7,968	3,992	1,648	716
Percentage of reports	100	6.64	3.33	1.38	.60
Percentage of poisonings		100	50.1	20.6	9.0

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previous study; some analysis is added for the sake of continuity.

All cases of poisoning are viewed and reported by the medical examiner of this state, since they are included in the Rules of Practice by definition:

> Medical Examiners will investigate and certify to all deaths supposably due to injury. These include not only deaths caused directly or indirectly by traumatism (including resulting septicemia), and by the action of chemicals (drugs or poisons), thermal, or electrical agents, and deaths following abortion, but also deaths from disease resulting from injury or infection related to occupation, the sudden deaths of persons not disabled by recognized disease, and those persons found dead.

This rule and its strict execution ensure that all cases of poisoning occurring in this state are listed in the material that we investigated.

Considerable uncertainty exists, however, with regard to alcoholism. In many cases it is almost impossible to decide if a decedent, known to have been drinking excessively, actually died *from* alcohol poisoning or succumbed to an ailment *during* his abuse of alcohol. Furthermore, acute alcohol death may occur in persons who have no record of abuse. Finally, the psychiatric concept of alcoholism as a true addiction to alcohol is distinct from heavy drinking of alcohol. Chemically demonstrated alcohol in blood at autopsy may, if found in excess quantities, indicate that acute alcohol poisoning is the cause of death. Sublethal quantities merely show that the person had ingested alcohol before he died, without necessarily being an alcoholic. Physicians attending private patients who die of alcoholism very often certify that death is due to organic disease of the heart or some other similar cause, their belief being that the family should not suffer from the stigma attached to death from alcoholism. If the physicians certify that death is due to alcoholism, the health department, under the Massachusetts law, should refer the case to a medical examiner. Many medical examiners are inclined to hide the actual cause when such cases are called to their attention — by certifying that death is due to cardiac failure, chronic nephritis or other natural cause, and the alcoholism is then recorded as a secondary cause. Vital statistics are compiled from certified primary causes; alcoholism appears less often in the statistics, as a result of this practice.

Autopsies are performed in only some viewings by the medical examiner — more frequently in Suffolk County (Boston), where 25.1 per cent of the views are combined with autopsy; in the other 14 counties the autopsy frequency ranges from 8.6 to 2.2 per cent.

In Suffolk County, alcoholics are generally treated at the Boston City Hospital or in hospitals specializing in alcohol or drug addiction. In the cases not so treated, such as deaths in lodging houses or persons found dead, police evidence concerning habits, usually corroborated by collections of full or empty liquor bottles, post-mortem examination and chemical examination of blood or brain or both or the removal and chemical examination of heart blood and (in some cases) urine furnish the basis for the certification of the death. It is only under these conditions that statistics of alcoholic deaths record the facts.

Results

The medical examiners investigated 119,838 deaths in the eleven-year period 1938–1948, or 20.9 per cent of the total deaths in the state. This percentage is higher for males than for females — 24.5 per cent of all male deaths are investigated, as contrasted to 14.7 per cent of all female deaths. Dead persons five to thirty-nine years old are viewed by the examiners more frequently (30 to 50 per cent) than are those of other ages, as deaths in the younger age groups are more often due to violence.

Table 1 shows the number of deaths due to poisoning according to the original certificates. They are 6.64 per cent of all views. Half the deaths due to poison (50.1 per cent) are alcoholic deaths; the

Table 1 (*Concluded*).

Year	Nontherapeutic Drugs			Sedative Drugs		Other Therapeutic Agents	
	Organic	Inorganic	Composite	Barbiturates	Other Sedatives	Anesthetics	Other
1938	26	28	6	22	9	33	4
1939	30	33	12	22	5	36	13
1940	33	38	12	32	5	37	3
1941	29	27	17	40	1	37	8
1942	19	25	5	28	6	37	3
1943	24	20	6	28	11	36	5
1944	20	19	11	22	5	40	6
1945	26	22	5	39	15	39	8
1946	23	32	3	49	10	37	7
1947	21	23	10	52	7	36	11
1948	18	35	13	43	4	44	6
Totals	269	302	100	377	78	412	74
Percentage of reports	.22	.25	.08	.31	.07	.34	.06
Percentage of poisonings	3.4	3.8	1.3	4.7	1.0	5.2	.9

remainder are due to a variety of chemicals, of which illuminating gas and carbon monoxide constitute the majority (59 per cent) of poisons other than alcohol. The relative importance of each category is illustrated in Figure 1, in which the annual mortality

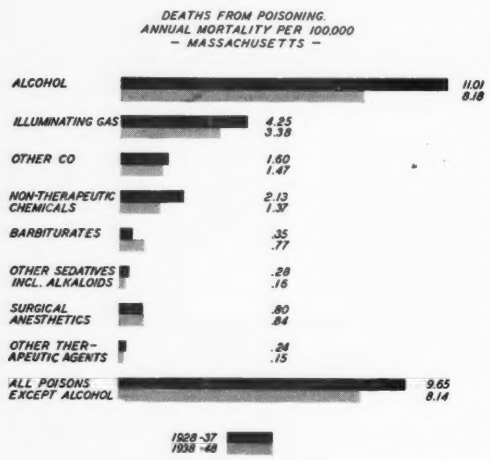

FIGURE 1. *Annual Mortality from Poisonings in Massachusetts per 100,000 Population.*

per 100,000 persons in Massachusetts is indicated. A comparison with the mortality figures for the previous decade, obtained by identical technics, is found on the same graph. The relative public-health importance of these mortality data is brought out by the fact that the mortality of all infectious diseases, except tuberculosis (International List 020-130) in Massachusetts was 6.9 per 100,000 in 1949 and 21.4 per 100,000 in 1943, with an average of 13.0 for that seven-year period. Assuredly, the mortality of 16.3 from poisonings deserves mention.

Alcohol Deaths

The 4131 deaths in which alcoholism was mentioned on the death certificates of the medical examiner are classified in Table 2 according to primary and associated causes of deaths. Only 1555 (or 37.7 per cent) deaths appear in the annual report as deaths from alcoholism. Alcoholic subjects were involved in 71 suicides and 419 accidents due to other causes than poisoning. Among the 3976 deaths from poisoning, 139 were also cases of alcoholism. A separate report is devoted to alcoholism in deaths from poisoning.[4] The remaining 1947 deaths regarded by these investigators as deaths due to ingestion of alcohol appear in the annual report under other categories. Examples of formulation of the certificates will illustrate why alcoholic deaths are often thus classified: "Edema of the brain (presumable) and other effects of the use of alcohol"; "Acute and chronic myocarditis and other effects of the use of alcohol"; "Natural causes, character indeterminate, plus the effects of the use of alcohol"; "Asphyxia (postural), and other effects of the use of alcohol"; or "Exhaustion and other effects . . . ." In most of these cases no autopsy was performed. As previously stated,[1] our classifications of such conditions as alcoholism are in accord with the findings obtained in mortuaries in which autopsies were performed regularly.[5, 6]

Carbon Monoxide

Carbon-monoxide poisoning constitutes the next largest group, with illuminating gas causing about two thirds of these deaths. Grouping of carbon-monoxide poisoning is not always consistent; a fair number of deaths are certified as such without indication of source.

TABLE 2. *Deaths Certified by Medical Examiners with Mention of Alcoholism, by Primary and Secondary Cause: Massachusetts, 1938-1948.*

YEAR	ALCOHOL REPORTED AS PRIMARY CAUSE	OTHER PRIMARY CAUSES REPORTED				TOTAL
		SUICIDE	ACCIDENTS	POISONING	OTHER	
1938	166	8	52	11	228	465
1939	185	6	62	5	168	426
1940	168	7	27	16	149	367
1941	164	10	42	13	162	391
1942	160	9	49	7	210	435
1943	127	5	60	8	196	396
1944	105	5	28	6	149	293
1945	135	4	15	13	170	337
1946	102	0	38	20	177	337
1947	121	13	28	20	168	350
1948	122	4	18	20	170	334
Totals	1555	71	419	139	1947	4131
Percentage	37.7	1.7	10.1	3.3	47.2	100

Toxic and Therapeutic Substances

These substances have been listed in 4 categories, with some subdivisions. In order of frequency, these groups are: nontherapeutic chemicals (mortality 1.37); sedative drugs (mortality 0.93);

surgical anesthetics (mortality 0.84); and other therapeutics (mortality 0.15). The individual substances are fully enumerated in Tables 3, 4, 5 and 6.

The first group (Table 3) contains such chemicals as are not dispensed for oral use or for use by injection. In the subgroup of inorganic poisons, which is the largest, cyanides, mercurials and arsenicals contribute equally to about half the deaths. Of the organic poisons, methyl alcohol and mixtures containing alcohol[1, 4, 7] form the majority, together with organic acids. The composite poisons vary, with no predominant single substance.

Among the sedative drugs (Table 4) barbiturates are in striking majority, accounting for 377 deaths of the 455 poisonings from sedatives. Only 46 deaths were due to alkaloids. Of the remaining 28, paraldehyde and chloral account for several deaths. Only 4 deaths were attributed to bromide, all apparently accidental. Mention of these 4 cases is of some interest, since the toxicologic importance of bromides is often exaggerated.

Bromide poisonings. 1. A forty-nine-year-old woman used bromides for the relief of nervousness and took this medication to excess. It is not stated whether the medication was prescribed or whether it was self-medication.

2. A seventy-one-year-old woman was suffering from arteriosclerosis and obesity. Her death was certified as due to "bromidism, therapeutic."

3. A fifty-four-year-old waitress was admitted to the Boston City Hospital in coma and died without recovering consciousness. The death certificate characterized her as an old morphine addict seeking substitutes, adding the note "overdose of bromides?"

4. A forty-six-year-old nurse who was given (by prescription) a three-week supply of bromides

TABLE 3. *Nontherapeutic Chemicals Listed as Causes of Death.*

No. of Cases	Organic Poisons
79	Alcohols: alcohol poisoning 2, creolin and rubbing alcohol 1, denatured alcohol 4, iodine and alcohol 1, medicated alcohol 1, menthol and alcohol 1, methyl alcohol 60, rubbing alcohol 5, wood alcohol 4
71	Organic acids: acetic acid 1, boric acid 1, carbolic acid 11, creolin 2, creolin-like substance 1, creosote 3, cresol 3, formalin 2, formaldehyde 4, glacial acetic acid 1, hydrocyanic acid 1, hydrocyanic-acid gas 2, lysol 27, phenol 7, salicylic acid 1, sulfonaphthol 4
15	Nicotine: nicotine 14, nicotine sulfate 1
40	Oil of wintergreen 31, methyl salicylate 8, wintergreen and camphor 1
20	Carbon tetrachloride 16, carbon-tetrachloride fumes 4
14	Kerosene 8, gasoline 1, range oil 5
4	Turpentine 4
12	Benzol 11, benzene 1
14	Miscellaneous: caustic bleaching water 1, chlorinated hydrocarbon 1, cyanogen gas 1, ethylene glycol 3, iodoform 1, naphtha explosion 1, oxydol 1, phosgene gas 1, salicylate compound 1, sewer gas 2, strychnine (rat poison) 1
269	
100	Composites: cockroach powder 4, Bugaside 1, drug poisoning 14, Energine 1, food poisoning 3, fruit from recently sprayed trees 1, fumes from acetylene torch 1, fumes from unknown solution 1, furniture polish 1, insecticide 3, liniment 1, mushrooms 5, pills for abortion 2, pine oil 1, plastic cement 1, poison 35, poisonous gas 5, Rough-on-Rats 3, Rustanol 1, soap 1, solvents 1, superheated gas 3, unknown substance 3, Vicks Vaporub 1, unknown weed 7
	Inorganic Poisons
49	Cyanides: cyanide 21, cyanide gas 2, cyanide potash 3, sodium cyanide 6, cyanogen 3, potassium cyanide 14
49	Mercurials: bichloride of mercury 34, mercurial poisoning 4, mercury 1, denatured alcohol and mercury 1, corrosive sublimate 7, mercuric chloride 1, mercuric chloride and potassium chloride 1.
42	Arsenic: arsenic 26, arsenate of lead 2, sodium arsenate 1, Paris green 11, arsenic trioxide and corrosive sublimate 1, sulfur of lime and arsenate of lead 1
62	Elements: phosphorus 22, lead 28, phosphorus and sodium fluoride 1, chromium 1, manganese 1, beryllium 3, sulphur 1, iodine 5
16	Inorganic acids and their fumes: hydrochloric acid 7, muriatic acid 1, nitric acid 4, sulfuric acid 4
37	Bases: household ammonia 12, lye 19, ammonia fumes 2, ammonia and sodium fluoride and kerosene 1, Drano 3
44	Other salts: sodium fluoride 35, sodium nitrate 3, potassium permanganate 1, fluoride 2, fluosilicate 1, aluminum chloride 1, potassium bichromate 1
3	Miscellaneous: sodium hydrate 1, bichloride of mercury and strychnine and mercurochrome 1, sulfur-dioxide inhalation 1
302	
269	Organic poisons
100	Composite poisons
671	Total number of cases

TABLE 4. *Sedative Drugs Listed as Causes of Death.*

No. of Cases	
377	Barbiturates: Barbital 6, barbiturate 170, barbituric acid 2, Carbital 1, Delvinal sodium 1, Luminal 12, Nembutal 28, pentobarbital 2, phenobarbital 114, phenobarbital and amytal 1, ortal sodium 1, seconal 16, sodium amytal 15, sodium barbital 1, Tuinal 2, veronal 4, veronal and sodium amytal 1
46	Alkaloids: alkaloidal poisoning 1, codeine 3, codeine and nembutal 1, laudanum 1, heroin 1, morphine 27, morphine and barbital 1, morphine and codeine 1, morphine and seconal 1, morphine and sodium amytal 1, morphine sulfate and nitroglycerin 1, opium 2, sleeping powder containing opium 2, Pantopon 1, paregoric 2
13	Paraldehyde 12, paraldehyde and nembutal 1
7	Chloral: Chloral 1, chloral hydrate 5, chloral hydrate and bromide 1
4	Bromides 4
8	Undefined sedative drugs: narcotic 1, drug addiction 1, marijuana 1, sedative 5
455	

TABLE 5. *Anesthetics Listed as Causes of Death.*

No. of Cases	
152	Ether 152
23	Nitrous oxide 10, gas oxygen 12, gas anesthesia 1
86	Spinal: curare 1, novocain and Pontocaine 5, nupercaine 1, Pontocaine 18, procaine 2, protocaine 6, procaine hydrochloride 1, spinal anesthesia 52
62	Anesthesia, unspecified, 62
9	Chloroform 8, chloroform and methyl salicylate 1
28	Ether and avertin 2, ether and cyclopropane 1, ether and gas oxygen 6, ether and oxygen 2, gas and ether 11, gas and oxygen and ether and sodium pentothal 1, Metycaine and ether 1, nitrous oxide and oxygen and ether 2, pentothal and ether 1, sodium pentothal and ether 1
16	Novocain 14, cocaine 1, Monocaine 1
7	Cyclopropane 7
3	Avertin 1, Evipal 2
2	Ethyl chloride 2
14	Sodium pentothal 13, thiobarbiturate 1
5	Intravenous anesthesia 1, intratracheal anesthesia 1, local anesthesia 2, vapor anesthesia 1
1	Morphine and scopolamine and Metycaine 1
1	Sodium amytal and morphine and scopolamine and novocain and Pontocaine 1
1	Nembutal and morphine and scopolamine and novocain and Pontocaine 1
1	Protocaine and Nembutal and morphine 1
1	Paraldehyde anesthesia 1
412	

for the treatment of chorea died after taking the entire amount of the prescribed medication in a few days.

Among surgical anesthetics (Table 5), ether caused about one third of the deaths; spinal anesthesia and unspecified types of anesthesia, comprising various mixtures and combinations of anesthetics, are equal to ether in number.

TABLE 6. *Other Therapeutic Agents Listed as Cause of Death.*

No. of Cases	
11	Strychnine: strychnine 9, strychnine sulfate 2
13	Arsenicals: arsphenamine 6, neoarsphenamine 6, sulfarsphenamine 1
2	Cinchophen 2
4	Aspirin: Anacin 1, aspirin and other drugs 1, acetylsalicylic acid 2
10	Sulfonamides: sulfanilimide 3, sulfadiazine 5, sulfathiazole 2
30	Miscellaneous: aminophylline and ephedrine and amytal 1, *Aspidium oleoresinae* 1, atropine 1, barium 2, decholin 1, digitalis 1, ephedrinal, epinephrine 1, ferrous sulfate 1, glucose solution with thiamine hydrochloride 1, Iodeikon solution 1, insulin 10, insulin and metrazol 1, Mercupurin 2, quinine 2, phenylhydrazine 1, Sodium Mandelate 1, sodium tetraiodophenolphthalein 1
4	Unknown drugs: inoculation for hay fever 1, injection 1, vaccine 1, serum 1
74	

Other therapeutic substances (Table 6) include a broad variety of drugs; sulfonamides, new for this period, account for 10 deaths, whereas antisyphilitic arsenicals have decreased in frequency. Therapeutic strychnine in the last years caused only one fourth of the deaths due to this agent in the previous ten years.

Suicides Among Deaths from Poisons

Somewhat over half the deaths from poisoning were noted as self-inflicted deaths. The problem of prevention of poisonous death is, therefore, complicated by the high component of suicides. To deal with accidental poisoning alone from a preventive standpoint would, however, be inaccurate, because of the difficulty with which the suicidal intention is ascertained. Suicide, in the public mind, has a stigma similar to that of alcoholism, and concealments are not infrequent. Moreover, willful ingestion of certain drugs in overdose is often indistinguishable from suicidal intent. Our fourth case of bromide poisoning is a case in point. Addicts may have a drive toward escape that is tantamount to suicide, although death in many cases would be termed accidental.

The percentage of suicides ascribed to poisoning is, however, consistent for each type of agent. Table 8 presents the number of deaths from poisoning by suicide, accident and homicide. Poison was chosen as a means in 2114 of 5717 (37.0 per cent) suicides occurring in Massachusetts from 1938 to 1948, whereas it was merely the *cause* of 1804 accidental deaths out of 28,594 (6.3 per cent) for the same period. There were 664 homicides, of which only 22 were carried out by means of poison. In other countries where firearms are less freely available than in this country, poisons account for more than 80 per cent of suicides.[7]

Carbon monoxide, barbiturates and inorganic poisons such as cyanides and arsenic are most frequently used in suicide. Anesthetics are only rarely used, as are alkaloids, both agents being under strict medical control.

The trend in relative frequency of suicide has not changed significantly (Table 8) during the eleven-year period studied. The drop in frequency of suicide in 1943–1944 is consistent with the general decrease of suicides in wartime.[7]

TREND OF DEATHS FROM POISONING, 1928–1948

The over-all trend of decrease in poisonous deaths is indicated in Figure 1, in which the mortalities of the last two decades are compared. A 10 to 50 per cent decrease is seen in all categories of agents, other than barbiturates. The apparently insignificant decrease in this category should in several instances be weighted with increased community consumption of the agents. Thus, deaths from illuminating gas have decreased from 234 in 1928 to 140 in 1948, although the household consumption of gas in Massachusetts rose from 25,000,000,000 to 43,000,000,000 cubic feet during the same twenty-one years.* Surgical anesthetics caused about the same number of deaths in two decades,

TABLE 7. *Deaths from Poison, by Motivation.*

	SUICIDES	ACCIDENTS	HOMICIDES	UNKNOWN	SUICIDES PER CENT
Illuminating gas	1080	535	11	22	65.5
Other, carbon monoxide	452	245	5	14	63.1
Inorganic poisons	199	103	—	—	65.9
Organic poisons	77	192	—	—	28.6
Composite poisons	45	53	2	—	45.0
Barbiturates	224	151	2	—	59.4
Other sedatives	20	58	—	—	25.6
Anesthetics	10	402	—	—	2.5
Other therapeutic agents	7	65	2	—	10.4
	2114	1804	22	36	53.1

*Data provided through courtesy of the Massachusetts State Department of Public Utilities.

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although, of course, the frequency of the use of anesthetics has increased measurably. Some decrease in deaths from certain poisons is unquestionably due to better control of the distribution, storage and handling of the materials. Cyanides and mercurials in the later period caused one third

Summary

Deaths from poisonous substances were reviewed on the basis of 119,838 deaths certified by medical examiners in Massachusetts from 1938 to 1948. Poisons were the cause of death in 7968 or 6.64 per cent of these cases; this corresponds to an annual mortality of 16.32 per 100,000. Half of these deaths were due to alcohol and were found to account for about 2.8 times more deaths than are listed as such in official reports. Poisonous gas accounts for 30 per cent, with illuminating gas as the most important source. The remainder constitutes a great variety of substances, of which a little less than half are agents not used in medical therapy. The two most important therapeutic groups are barbiturates and anesthetics.

Well over 50 per cent of deaths from poison are suicidal. Of all suicides, poisons cause 37 per cent. More deaths from carbon monoxide, barbiturates, cyanides and arsenic are suicides than are deaths from other poisons.

The trend in deaths from poisoning generally shows a significant decrease in many categories, despite increased community consumption of the various agents. Only deaths from barbiturates are

TABLE 8. *Trend in Deaths from Poisoning by Suicides and Accidents: Massachusetts, 1938–1948.*

YEAR	TOTAL	SUICIDES	ACCIDENTS	HOMICIDES	UNKNOWN	SUICIDES %
1938	361	205	148	1	7	56.8
1939	393	225	163	2	3	57.4
1940	396	225	170	1	0	56.9
1941	363	220	136	3	4	60.5
1942	296	168	121	2	5	56.8
1943	337	151	185	1	0	44.7
1944	340	154	180	3	3	45.3
1945	381	184	189	2	6	48.4
1946	380	193	180	2	5	50.8
1947	370	181	185	1	3	49.0
1948	359	208	147	4	0	58.0
Totals	3976	2114	1804	22	36	53.1

of the deaths from these agents that occurred from 1928 to 1937.

Barbiturates show the only significant and ominous increase that has taken place in this period. Figure 2 shows that the number of deaths from barbiturates rose 4.9 times in the period, whereas the suicides from barbiturates rose no less than 11.6 times. There is no doubt that public control of these sedatives lacks the necessary stringency, and there is general recognition that the availability of barbiturates is largely due to illegitimate sales beyond the control of the medical profession.

In contrast to barbiturates, the decrease in deaths from the alkaloid group of sedatives is shown at the right in Figure 2. The number of deaths in 1928 was 3.8 more than those in 1948, whereas the suicidal cases decreased 1.8 times. Alkaloids are undoubtedly submitted to more rigid control than are any other therapeutic agents, and the decrease in accidental and suicidal deaths therefrom reflects the effectiveness of the control. A serious question may arise in the future with increased synthetic (hence less controllable) production of morphine derivatives like methadon and of analgesics such as Demerol (meperidine). No such agent was mentioned in the material studied.

Deaths from alcoholism have decreased, according to both officially reported figures and the larger figures that were obtained during this study. Although the trend of alcohol consumption, in terms of amounts of ethyl alcohol, has not decreased appreciably, there has been a considerable change in vehicles, with beer consumption almost doubling in ten years at the expense of a decrease in the use of concentrated liquor.[8] When such changes in beverage occur the lethal aspects of alcoholism will usually decrease.

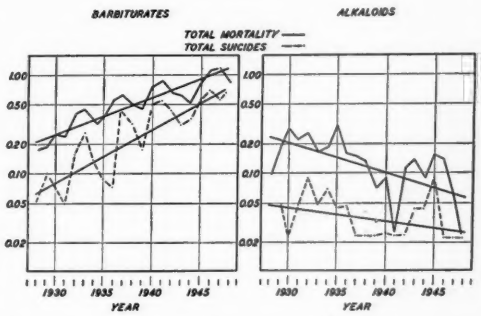

FIGURE 2. *Annual Mortality per 100,000 Population from Barbiturates and Alkaloids: Massachusetts, 1928–1948.*

steadily increasing — at a rate that indicates the need of more effective control of their distribution.

We wish to thank Mr. Edward J. Cronin, Secretary of the Commonwealth, and Mr. James F. Kane and Mr. Leo Flaherty of the Archives Division, for their co-operation in placing the original records at our disposal. We also wish to thank Miss Alene W. Mills for her valuable collaboration in record research and statistical enumeration of the material.

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AUREOMYCIN IN THE TREATMENT OF DIFFUSE PERITONITIS*

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BOSTON

In a previous communication aureomycin or a combination of aureomycin and penicillin was reported as effective in the treatment of diffuse peritonitis of intestinal origin.[1] Our results in 24 cases demonstrated that aureomycin alone was superior to penicillin alone in such infections. This report deals with the effects of aureomycin therapy in 59 additional patients with diffuse peritonitis.

Clinical Observations

The therapeutic response of 59 patients with diffuse peritonitis of intestinal origin was observed (Table 1). The bacteria isolated from the peritoneal exudate were *Escherichia coli* in 23, staphylococci in 17, *Bacillus proteus vulgaris* in 9, *Pseudomonas aeruginosa* in 8, streptococci in 5, paracolon bacilli in 3, *Aerobacter aerogenes* in 2, diphtheroids in 2, *Klebsiella pneumoniae* in 2, clostridia in 2 and *Micrococcus tetragenus* in 1. In 26 patients there were 2 or more bacterial species; in 16 only 1 was cultured. In 14 cases grossly purulent exudate was present; leukocytes and bacteria were seen on smear, but cultures were sterile. This may have been due in part to the antibacterial effect of aureomycin, which was administered intravenously from four to twenty-four hours before operation to 7 of these patients.|| No culture was obtained in 3 cases.

Aureomycin hydrochloride buffered with sodium glycinate was administered intravenously to all patients during the acute phase of the disease. The usual dosage was 500 mg. of the drug dissolved in 500 cc. of isotonic saline or dextrose solution twice daily. Patients with fulminating infections received 500 mg. of aureomycin every six to eight hours. In such cases the infusions were usually given by a modified Duffy technic,[4] using polyvinyl plastic tubing** fitted with a Tuohy adapter and placed in the subclavian vein via the median basilic vein.[5] When the disease process was controlled, parenteral therapy was replaced by the oral route or by penicillin.

Forty-seven of the 59 patients showed an excellent and rapid response to aureomycin therapy (Table 1), with a simultaneous regression in the signs and symptoms and a rapid uneventful convalescence in all but 3. Such a favorable response was usually observed within forty-eight hours after the institution of therapy. There were three complications in this group. One patient with peritonitis due to a gangrenous perforated gall bladder developed a subhepatic abscess ten days after cholecystectomy. Recovery followed drainage of the abscess and continued administration of aureomycin. A patient with appendiceal peritonitis developed a sterile pleural effusion, and a third with peritonitis due to volvulus of the sigmoid had pneumonia on the eighth postoperative day. Both recovered on continued aureomycin therapy.

Aureomycin was particularly effective in the cure of peritonitis of appendiceal origin (19 of 19 patients), in peritonitis due to perforated peptic ulcer (7 of 8 patients) and in peritonitis associated with gangrenous cholecystitis (4 of 5 patients).

In 6 patients, the role of aureomycin in the cure of the infection could not be definitely assessed. They all survived, but improvement was either slow or possibly attributable to other therapeutic measures, such as drainage of abscesses,[3] or to other antibiotics.

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||Aureomycin rapidly reaches peritoneal fluid after intravenous administration.[2] In experimental peritonitis in dogs treated with aureomycin, bacteria present in the smear of the peritoneal exudate frequently failed to grow in culture.

**Obtained from Becton Dickinson Company, Rutherford, New Jersey.

One patient with peritonitis following perforation of a gangrenous gall bladder failed to respond to aureomycin. *B. proteus vulgaris*, cultured from the peritoneal exudate, was resistant in vitro to aureomycin but sensitive to Chloromycetin. Aureomycin was omitted and Chloromycetin given through a Miller–Abbott tube. Recovery followed slow convalescence complicated by dehiscence of a grossly infected wound.

The remaining 5 of the 59 patients died — one with hypertension, congestive heart failure, nephrosclerosis, uremia, fulminating uremic enterocolitis and multiple perforations of the ileum; one penicillin alone. In several cases in which the response to aureomycin was slow or doubtful, the addition of penicillin had no salutary effect. Furthermore, in-vitro studies[6] indicate the existence of a possible antagonism between penicillin and aureomycin. The growth of several strains of *E. coli* and *Staphylococcus aureus* was inhibited to a greater extent by either drug alone than by a combination of the two drugs in the same concentration.

Toxicity

Gastrointestinal side-effects occurred in 12 patients (20 per cent). Of 9 patients with diarrhea,

Table 1. *Effect of Aureomycin in 59 Cases of Diffuse Peritonitis.*

Source of Infection	No. of Cases	Results		
		Good	Doubtful or Poor	Died
Appendix*	19	19	0	0
Postoperative				
After resection of colon for carcinoma	5	0	2	3
After gastrectomy for peptic ulcer	2	0	1	1
After intraperitoneal closure of colostomy	1	1	0	0
After paracentesis	1	1	0	0
Gangrene and perforation of strangulated small bowel due to postoperative adhesions	1	1	0	0
Small intestine				
Perforated peptic ulcer	8	7	1	0
Perforated Meckel's diverticulum	1	1	0	0
Strangulated incisional hernia	1	1	0	0
Uremic enterocolitis and perforation of ileum	1	0	0	1
Large intestine				
Perforation of cancerous bowel	3	3	0	0
Ulcerative colitis with perforation	1	1	0	0
Volvulus of sigmoid	1	1	0	0
Mesenteric thrombosis	1	1	0	0
Gall bladder				
Gangrenous cholecystitis	5	4	1	0
Bile peritonitis following cholecystectomy	2	1	1	0
Miscellaneous				
Pancreatitis	2	1	1	0
Twisted ovarian cyst	1	1	0	0
Pyosalpinx	1	1	0	0
Biliary cirrhosis — ascites	1	1	0	0
Visceral perforation by rubber splint at pancreaticojejunostomy	1	1	0	0
Totals	59	47	7	5

*Nine of these patients had localized abscesses in the right lower quadrant or pelvis in addition to diffuse peritonitis.

with peritonitis, fecal fistula, intra-abdominal abscesses and wound infection that followed resection of the transverse colon for carcinoma; and one with a neglected leak from the duodenal stump after gastrectomy for peptic ulcer. The other 2 patients developed peritonitis after the resection of the colon for carcinoma. Aureomycin effectively controlled the infection in these 2 patients, but they died of aspiration pneumonia and myocardial infarction respectively.

Of the 47 patients who responded favorably, 31 received aureomycin as the only chemotherapeutic agent. Eight were shifted to aureomycin after failure to respond to penicillin. Two responded only after aureomycin was added to penicillin. The remaining 6 patients received aureomycin and penicillin from the beginning of therapy. The therapeutic response to aureomycin alone was as good as that to penicillin and aureomycin combined and was clearly superior to the response to

2 had protracted watery diarrhea that required energetic fluid and electrolyte therapy. Diarrhea was encountered in patients who received aureomycin intravenously (4) as well as in those given it orally (5). This may be related to the excretion of the intravenously administered drug (via salivary glands and bile) into the gastrointestinal tract, as suggested by the partial suppression of the normal fecal flora in patients receiving aureomycin intravenously.[7] Cultures of diarrheal stools failed to yield specific pathogens or staphylococci, to which some cases of diarrhea following aureomycin have been attributed.[8]

Three patients, 2 of whom had diarrhea, also developed stomatitis and esophagitis characterized by dysphagia, substernal and epigastric pain and burning. These symptoms subsided several days after discontinuance of aureomycin and were refractory to therapy. Two other patients had nausea; 1 of them vomited. Repeated intravenous infusions

uniformly resulted in a painless thrombotic occlusion of the vein. Each vein was used for 2 to 4 infusions before becoming thrombosed.

The parenteral administration of vitamin B complex and folic acid appeared to have no noticeable effect on the gastrointestinal symptoms. There was no apparent correlation between nutritional status, dosage or duration of therapy and the incidence or severity of gastrointestinal symptoms. In most cases, however, gastrointestinal symptoms were mild and disappeared promptly after therapy was stopped. Treatment in several severely ill patients was continued in spite of diarrhea until the infection was controlled. No other toxic reactions were observed.

Discussion

Excellent results have been reported in the treatment of diffuse peritonitis[9, 10] with penicillin even in cases in which gram-negative intestinal bacteria predominated. Since peritonitis of intestinal origin is considered a mixed infection, the virulence of which is due to the combined action of the various bacteria, the gram-positive species have been regarded as the essential pathogens because of the favorable action of penicillin.[10]

Since excellent results have likewise been reported with aureomycin in the treatment of peritonitis,[1, 11-14] penicillin and aureomycin in combination have been suggested as the most effective antibiotic therapy in such infections.[15, 16]

The results herein reported indicate that aureomycin alone is more effective than penicillin alone and at least as effective as aureomycin and penicillin combined. Eight patients responded to aureomycin after penicillin had failed to control the infection; 2 others recovered only when aureomycin was added to initial penicillin therapy. Those patients who failed to respond satisfactorily to aureomycin alone did not improve after combined antibiotic therapy or massive penicillin therapy alone.

Thus, our data suggest that aureomycin is more effective than penicillin in the treatment of diffuse peritonitis. Its superiority to penicillin stems from its antibacterial action against both gram-positive and gram-negative bacteria, the infrequent and slow development of bacterial resistance and its activity in the presence of exudate.

It has been reported that aureomycin may interfere with the antibacterial action in vitro of penicillin.[17, 18] Mixtures of varying composition of aureomycin and penicillin exhibited less effective action against strains of hemolytic staphylococci, streptococci and *Kl. pneumoniae*[17, 18] than did either drug alone. Such antagonism has also been reported for Chloromycetin and terramycin when combined with penicillin.[18-22] Whether this also occurs in clinical therapy cannot be determined from available data. The possibility that this may be so should restrict the use of combined antibiotic therapy unless definite synergistic action can be demonstrated, as in the case of aureomycin and streptomycin in the treatment of brucellosis.[23]

Summary

Aureomycin was remarkably effective in the treatment of diffuse peritonitis of intestinal origin in 59 patients. The response was excellent in 47, doubtful in 6 and poor in 1. Five other patients died, although in 2 the infection was effectively controlled. In most cases the convalescence was rapid and wound healing as fast as if no infection had been present. Aureomycin is superior to penicillin in the treatment of peritonitis. There was a significant incidence (20 per cent) of gastrointestinal toxicity such as stomatitis, esophagitis and diarrhea. No other toxic effects were noted.

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THE TUBERCULOUS DIABETIC PATIENT*

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A total of 3178 patients with pulmonary tuberculosis were admitted to the Uncas-on-Thames Tuberculosis Hospital from July 1, 1937 to July 1, 1950. Of these, 68 or 2.1 per cent had associated diabetes mellitus. This study is concerned with the course of tuberculosis in these diabetics and with their present status.

Many writers believe that some peculiar relation exists between diabetes mellitus and tuberculosis and that the diabetic is more prone to develop tuberculosis than is the nondiabetic. Banyai,[1] Root[2] and Neogy and Ray[3] state that the prevalence of tuberculosis is more than three times as high among diabetics than among the general population. Root and Bloor[4] showed that the frequency of pulmonary tuberculosis in diabetics at autopsy appears to be at least 2 to 4 times as great as it is in nondiabetics. Root and Bloor[4] have also pointed out that the mortality from tuberculosis among diabetics shows no fall comparable with the fall in rate among the general population. The causes of the increased susceptibility of diabetics to tuberculosis and of these patients' poor resistance to their disease after it has developed (if this is true) are not known. Numerous explanations of this have been offered, but to date the answer is still conjectural. Hyperglycemia, acidosis, increased glycerol production, altered function of the leukocytes and tissues in general and lowered pulmonary concentration of phospholipids and lipids have all been advanced as possible causes.[4, 5]

Early recognition and prompt treatment of tuberculosis in the diabetic is, of course, of great importance if this condition is to be arrested in a higher proportion of diabetics than has heretofore been true. According to Fett,[6] the average life expectancy of a tuberculous patient with diabetes is barely half what is would be in one with tuberculosis uncomplicated by diabetes.

Tuberculosis discovered in the minimal stage in a diabetic is rare. This is shown in the literature and is corroborated by this study. Of the 68 patients discussed in this review, only 1 had minimal tuberculosis. Of the remaining 67 cases, 16 or 24.6 per cent were moderately advanced and 51 or 75 per cent were far advanced. Of the 68 patients, 53 have been discharged and 15 are still hospitalized. Of the 53 discharged, 35 are known to be dead, 2 are alive with active tuberculosis, the disease has been arrested in 11 for a period ranging from six months to nine years and 5 are untraceable. Of the 15 cases still hospitalized, 7 have active tuberculosis, unimproved, and the disease of 8 is active, improved. It would appear, then, that the prognosis for the patient with tuberculosis and diabetes is poor — and worse than for the patient with tuberculosis alone.

The diabetes did not militate against the use of any form of therapy for any of the patients in this study, and all forms of tuberculosis therapy were used as indicated. Usually, the diabetics with tuberculosis did not respond to treatment as well as did the non-diabetics. In the great majority of cases, the end result was either death or a long course of hospitalization with slowly progressing tuberculosis.

The x-ray appearance of the tuberculosis in this series of diabetics was not significantly different from that in nondiabetics.

The diabetes was mild in 11 per cent, moderate in 28 per cent and severe in 61 per cent of the cases. It was diagnosed prior to the discovery of tuberculosis in 47 or 69 per cent and after tuberculosis developed in 5 or 7 per cent of the cases. The two diseases were diagnosed together in 16 or 24 per cent of the total. Table 1 shows the duration of diabetes prior to the development of tuberculosis. Frequent routine x-ray examination of the lungs of all diabetics would uncover tuberculous lesions in earlier rather than advanced stages and might well improve the prognosis for their tuberculosis.

TABLE 1.* *Duration of Diabetes Prior to the Development of Tuberculosis.*

DURATION	NO. OF PATIENTS
yr.	
0–2	8
3–5	15
6–10	15
11–15	6
16–20	2
21–25	1

The blood sugar was kept below 150 mg. per 100 cc. wherever possible; this was achieved in the majority of cases. No significant relation was noted between the degree of control of the diabetes and the course of the patient's tuberculosis. The diabetic status of the 11 arrested cases was no different from that of the majority of the other 57 patients.

Table 2 shows the ages of the patients on admission. More than two thirds of the patients were over forty-four years of age. The older diabetic should not receive x-ray examination less frequently than others merely because of age.

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Table 3 shows how long those who died lived after their tuberculosis was diagnosed. Only 3 patients lived longer than six years; 50 per cent died within two years.

Conclusions

Of 3178 patients admitted to the Uncas-on-Thames Tuberculosis Hospital with pulmonary tuberculosis from July 1, 1937 to July 1, 1950, 68 or 2.1 per cent had associated diabetes mellitus.

Table 2. *Age of Patients on Admission.*

Age	No. of Patients
yr.	
Under 15	0
15–44	22
45–64	36
65 or over	10
Total	68

Of the 68 patients, 53 were discharged and 15 are still hospitalized. Of the 53 discharged, 35 are known to be dead, the disease has been arrested in 11 for periods ranging from six months to nine years, 2 are living with active tuberculosis and 5 are untraceable. Of the 15 patients still hospitalized, the disease of 7 is active, unimproved, and the disease of the remaining 8 is active, improved.

The prognosis for the tuberculous patients who have diabetes is graver than for the tuberculous patient who does not have diabetes.

All diabetics should have a chest x-ray examination at least every six months — or more often, if signs or symptoms warrant more frequent x-ray examination of the chest.

Table 3. *Duration of Life After Tuberculosis Was Diagnosed.*

Duration	No. of Patients
yr.	
0–1	9
1–2	10
2–3	5
3–4	5
4–5	
5–6	3
6–7	0
7–8	2
8–9	1

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MEDICAL PROGRESS

THE USE OF ACTH AND CORTISONE IN DERMATOLOGY

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PROBABLY the most important recent development in dermatologic therapy has been the availability of adrenocorticotrophic hormone and cortisone. With the startling announcements in the lay press of their remarkable curative powers, patients with acute or chronic dermatoses began requesting their therapeutic trial. These drugs, even in ointment form, are alleged in newspaper and magazine accounts to have cured almost all cutaneous eruptions, from simple eczema to pemphigus.

Medical literature has, fortunately, been more conservative. Various reports have shown how valuable co-operative work between dermatologists and internists has been in properly evaluating new drugs, and as a result definite progress has been made in this evaluation. The first reports described the astounding rapidity with which these compounds achieved results in skin disorders. It was not until later, when untoward physiologic effects were noted, that unfavorable reports appeared. We have now reached a more conservative estimate of both the bad and the good effects. Physicians have realized that most of the undesirable reactions are reversible and disappear with discontinuance of treatment. Moreover, they know that many of them will not occur if the patients are properly selected and overdosages avoided.

Before prescribing these drugs the physician should familiarize himself with the physiologic effects of ACTH and cortisone. These have been reviewed so often in recent literature that all physicians have had an opportunity to study them, and it is not necessary to discuss them here. As regards complications, Frawley[1] has outlined them thoroughly in a recent article, "Recognition and Prevention of the Complications of ACTH and Cortisone Therapy." He elaborates first on the physiologic changes associated with reduced adrenocortical function and on those related to excessive corticoid levels.

Early reports emphasized the occurrence of a Cushing-like syndrome,[2, 3] stressing the moon facies.

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In one series,[4] this sequela occurred in 9 out of 44 cases; in another[5] there were 4 such cases.

Early reports noted alterations in electrolyte metabolism, and most patients were given potassium chloride. With smaller doses, however, this hypopotassemia has appeared less often. Although necessary in some cases, the administration of large doses of potassium can be dangerous. Now, with smaller dosages and shorter courses of therapy, there are fewer reports of hypopotassemia and hypochloremic alkalosis.

The hyperglycemia in these cases was at first thought to contraindicate its use in diabetes. With the concomitant use of insulin, however, diabetic patients are now being given these drugs without serious effect. According to Frawley,[1] permanent diabetes following the use of ACTH or cortisone has not thus far been reported.

Various cerebral disturbances have been noted after use of these drugs, the most serious being the frank psychoses,[2, 4, 6] with suicide occasionally occurring during or on cessation of treatment.[7] Four convulsive seizures in twenty-four hours were noted by one writer,[8] and there are other similar reports. Of 40 patients treated with ACTH, 3 showed episodes of status epilepticus,[6, 9] and severe occlusive arterial phenomena have been found at autopsy.[10]

Thrombotic complications appear to be more likely to develop in persons with underlying vascular disease or with a history of previous thromboembolic disease. Cosgriff[11] found that among approximately 700 patients treated with corticotropin (ACTH) or cortisone, in 28 patients there have been 40 episodes of thromboembolic disease which have developed during or shortly following hormonal therapy. These vascular complications, together with the observations of hypercoagulability of the blood associated with the administration of these agents, indicate, according to Cosgriff, that thromboembolic phenomena should be considered as one of the serious complications of corticotropin and cortisone therapy.

Many cutaneous reactions have been noted — increased pigmentation,[4-6, 12] furunculosis,[4] hirsutism,[3, 5, 12] seborrheal dermatitis,[12] alopecia,[13-17] acne (a common complication),[2, 3, 5, 12, 14-17] atrophic striae[5,6] (permanent[3] in some cases), delayed wound healing[2, 5, 14-17] and flattening of keloidal scars.[5] Recurrences of herpes simplex have been noted in several patients.[2] Herpes zoster was noted in 3 patients, after treatment with ACTH in 2 cases and with cortisone in one.[2] Erythema multiforme with marked temperature and malaise was seen in 1 of 44 patients treated.[4]

ACTH and cortisone are contraindicated in hypertension, congestive heart failure, renal insufficiency, peptic ulcer, tuberculosis, syphilis, various psychoses, acute infections, diabetes mellitus, osteoporosis and arteriosclerosis. Peritonitis has been reported in patients given ACTH,[18] and Brunsting has emphasized that this condition often masks acute abdominal infections, as was emphasized in a recent editorial[19] in the *New England Journal of Medicine*. The deleterious effects of ACTH and cortisone on tuberculosis were stressed in a later editorial.[20] In cases of diabetes mellitus, these drugs should be used with great care and preferably only in hospitalized patients. Their use should be avoided if possible in women with a tendency to hirsutism.

Allergy and Hypersensitivity

Sprague[21] points out that "the relationship between adrenal cortical function and hypersensitivity has long been suspected. Consequently, the demonstration of the dramatic effect of cortisone and ACTH on rheumatic diseases immediately suggested the possibility that these hormonal agents might favorably modify the hypersensitive state. This has proved to be the case. In addition, cortisone and ACTH are proving to be useful tools for study of the mechanism of the hypersensitive state."

There seemed to be a fair possibility that the advent of these drugs would revolutionize previous concepts of allergy. According to Thorn and his co-workers,[2]

> It appears possible that the adrenal steroids alter the allergic tissue reaction that follows the union of antigen and antibody. One proved mechanism involved in this reaction is the demonstrated ability of these hormones to inhibit the formation of histamine and accelerate its breakdown. It appears that the action of ACTH and cortisone may dissociate the harmful effects of hypersensitivity from the beneficial reaction of immunity.

Selye[22] states that cortisone and purified ACTH inhibit the anaphylactoid reactions of the rat to the parenteral administration of egg white. Desoxycorticosterone acetate (a mineralocorticoid compound) and a highly corticotropic impure anterior-pituitary preparation failed to inhibit and even tended to aggravate this reaction. These observations are discussed in connection with the probable participation of the adrenal cortex in the pathogenesis of the allergic and other so-called collagen diseases.

Bordley and others[23] treated a patient with extensive urticaria due to penicillin. Within twenty-four hours all evidence of the sensitivity had disappeared. They also used ACTH to effect a rapid and complete recovery in a case of severe exfoliative dermatitis due to iodine. There was no relapse when the hormone was discontinued.

In a series of patients with allergic diseases reported on by Feinberg and others,[24] 1 with a severe bullous urticaria due to penicillin responded completely to ACTH in four days, but there was a recurrence ten days later; manifestations finally subsided completely with a second course of ACTH. This patient was given 630 mg. over a nine-day

period. Another patient with atopic dermatitis responded well initially to cortisone but relapsed when the drug was withdrawn. Another patient with urticaria and angioneurotic edema responded to an initial course of ACTH, but signs recurred a few days after the therapy was discontinued. The writers believe that in severe allergic manifestations of limited duration the use of these hormones may be helpful, since the remission may be long enough to cover the natural evolution of the disease. In acute lesions, however, the chances of coincidental spontaneous remission make interpretation of favorable hormonal effects hazardous. This is true, also, of such disorders as untoward reactions to penicillin and sulfonamides or seasonal allergic manifestations when the season is not too long.

In a series of 11 patients with intrinsic allergic dermatitis (eczema) treated with these drugs, Cooke and others [25] noted relief of pruritus in a few days, the skin appearing somewhat improved in a few cases. In all patients, however, the symptoms returned after cessation of therapy. In patients with urticaria the symptoms were similarly relieved and the lesions cleared, but both reappeared when treatment was discontinued. The rapid cure of a generalized external allergic dermatitis (due to Furacin), — accomplished in three days, — was believed to have been effected by hormone treatment. This paper, however, stresses the need for continued allergic control of these disorders, and I agree. In most of the cases I have seen, the cutaneous eruption reappeared on withdrawal of the medication. However, if established dermatologic therapy is employed in conjunction with hormone treatment, the effect is more likely to be lasting.

Coste and Oury[26] report from France that in a patient with chronic polyarthritis a gold dermatitis improved after a course of cortisone treatment, beginning with an initial dose of 300 mg. daily, followed by daily doses of 100 mg. and then lesser amounts. A relapse occurred five days after treatment ended, the patient improving again 18 hours after one injection of ACTH.

Kanee and others[27] reported on the striking results in a fourteen-month-old infant with generalized eczema and asthma of thirteen months' duration. Previous hospitalization had brought about no marked change in the appearance of the skin. A course of ACTH treatment was given, beginning with 10 mg. every six hours for the first forty-eight hours, then every eight hours. In twenty-four hours the skin showed marked improvement. In forty-eight hours there was virtually complete involution of the eczema. A slight flare-up occurred on the tenth day of treatment; on the fourteenth day lobar pneumonia developed. The hormone was discontinued, whereupon the eczema almost immediately became generalized. At this point the patient was given aureomycin. Five days later typical varicella appeared. After recovery from the two infections and reinstitution of ACTH therapy, 10 mg. every six hours for four days, there was a striking but less complete involution of the eczema. Two months later a few areas of eczema persisted on the face, neck and shoulders, but the over-all improvement was still maintained. No untoward reactions were noted.

Glaser and others[28] found both ACTH and cortisone to be effective in giving temporary relief to 3 patients with eczema. They also found that infants and children in general required larger doses in proportion to their body weight than did adults. The local use of cortisone ointment containing 250 mg. per ounce was found ineffective in 1 case of eczema.

Sulzberger and others[4] report a 75 to 100 per cent reduction of erythema, scaling and pruritus within one week of ACTH treatment for exfoliative dermatitis in 4 patients, 3 of whom, however, relapsed immediately after treatment was discontinued. The single exception was a patient who continued to receive maintenance doses. One of these patients developed an apparently allergic response to some component of the ACTH preparation, exhibiting during the course of treatment a multiform erythematous eruption with fever, malaise and arthralgia in addition to other symptoms.

Kierland and others,[29] although they believe that cortisone greatly improves acute urticaria from antibiotics and serum reactions, achieved no results with this drug in cases of chronic urticaria; in fact, 1 patient developed urticaria during treatment.

It is believed to be

> almost certain that prolonged administration of these drugs in children or adolescents would lead to serious changes, including growth disturbance. . .It should be added that in an acute allergic emergency (immediate serum reaction, anaphylactic shock or acute asthma) these hormones do not work rapidly enough to save the patient's life. . . .Pituitary adrenocorticotropic hormone and cortisone are useful measures in special allergic situations, but they should not be employed as a short cut to a careful diagnosis and more rational allergic therapy.[30]

Spies and Stone[31] discuss the local use of cortisone in various disorders that failed to respond to 3 different antihistaminic substances, used internally and locally. Of 2 cases of allergic dermatitis only 1 is described, supposedly a dermatitis venenata caused by a washing powder. The eruption was of three weeks' duration. An ointment containing 5 mg. of cortisone acetate per gm. was applied once daily and the area bandaged. The eruption disappeared completely in two weeks, the severe itching stopping within twenty-four hours of the first application.

Mandel and others[32] demonstrated that the effect of these drugs is not solely a psychic one. A twenty-eight-year-old man with eczematoid dermatitis and angioneurotic edema was given ACTH by continuous intravenous infusion for eight to twelve hours daily. When a placebo was substituted for the drug on the

third day a relapse occurred; this was controlled by resuming the infusions of ACTH. Also reported is dramatic improvement in a sixty-four-year-old man with a neurodermatitis that had been resistant to therapy for many years; in this case the result was achieved with continuous intravenous infusion of ACTH for eight to twelve hours daily.

I have been following a case of severe exfoliative dermatitis of over two years' duration. At first, treatment with both ACTH and cortisone brought prompt results. After each course of medication, however, the eruption promptly recurred, and each time the dosage has had to be increased. This man is still suffering from his exfoliative dermatitis and in addition has now developed marked psychotic disturbances that necessitated hospitalization. He is still receiving the hormones, for each time treatment is discontinued his eruption recurs and he daily shows increased fluid retention.

Atopic Dermatitis

Resistance to treatment has made atopic dermatitis, often called neurodermatitis, the bane of most dermatologists. With the advent of hormone therapy it was inevitable that most dermatologists and clinicians would seize on these drugs in an attempt to solve this problem.

Randolph and Rollins[33] described 4 cases of atopic dermatitis, all resistant to usual allergic therapy. The dermatitis, present since infancy (the patients' ages were thirty-one, six, six, and three and a half years), could be acutely exacerbated at will after the ingestion of one or more known allergic foods. The youngest patient was given a total of 1080 mg. of ACTH over a period of three weeks. In the others, treatment extended over three days only, the drug being given intramuscularly in divided doses. In all cases an acute exacerbation was intentionally induced prior to administering the hormone, and in all cases the dermatitis subsided completely or improved remarkably in one to three days. This improvement or apparent "cure" persisted for from two to ten days after the end of treatment, the dermatitis in all cases recurring in a more severe and extensive form than previously. After varying lengths of time (a few weeks to two months) the dermatitis subsided to the degree present prior to the ACTH therapy. No untoward symptoms were noted in those patients treated for three days. In the child treated for three weeks fluid retention developed, but when dosage was reduced from 20 mg. every six hours to 12 mg., 9.25 mg. and finally 3.25 mg. every six hours, the edema disappeared. The writers conclude that ACTH is an effective therapeutic agent in chronic atopic dermatitis and express the hope that it will be possible to determine the minimal effective dose of this hormone that will maintain the beneficial effects produced by short courses of ACTH therapy.

From Canada[27] comes the report of a fourteen-month-old infant in whom generalized atopic dermatitis had developed at the age of three weeks and recurring asthma had first appeared at twelve weeks. ACTH treatment produced a rapid and dramatic recovery from the eczema. These diseases tend to recur when therapy is discontinued, but in this case considerable clinical improvement was still evident after eight weeks. Transient intense pallor, listlessness and abdominal distention were the only clinical side-effects noted; these followed each injection of ACTH and were due to the oxytocin contaminant in the hormone. Since hereditary influence appears to be important in atopic persons, it has been suggested that an inherited endocrine deficiency or imbalance impairs their ability to inactivate histamine. The result is a periodic accumulation of histamine in susceptible tissues, such as the lungs, antral mucosa and skin, with the resultant clinical syndromes. The hypothesis is that this impairment of function can apparently be restored to normal during the administration of ACTH.

Having seen the results in several cases of atopic dermatitis treated by internists, I have developed perhaps too conservative an opinion of the value of these medications in this disorder. I was relieved to find at the recent meeting of the American Dermatological Association and the section meeting of the American Medical Association that most of the older dermatologists concurred in my opinion and had had similar experiences with these drugs. The excellent paper by Sternberg and others[34] epitomized this. They treated 24 patients with severe atopic dermatitis. Complete healing of the dermatitis with 200 to 300 mg. of cortisone, given either orally or intramuscularly, was seen in all but 1 patient, who was later relieved by ACTH. The intramuscular administration was more satisfactory than oral use, which required higher and more frequent doses. Topical application was found ineffective. Two patients developed a pustular dermatitis from the use of the ointment.

All patients relapsed on discontinuance of cortisone, irrespective of the method of terminating treatment. In the hope of maintaining the benefits with cortisone the dosage was gradually increased over a two-week period, but when the daily dose reached the range of 75-100 mg. most of the patients relapsed; all relapsed with doses below 75 mg. The second method, — of giving 200–300 mg. every second day, three times a week, and then twice weekly, — also failed. Tapering off the cortisone gradually for one week during which time ACTH was administered in a maximum dosage of 60 mg. daily was unsuccessful. In a rather large group, cortisone was gradually discontinued and the patients were given 1 or 2 gm. of pregnenolone acetate. All these patients relapsed as the cortisone was discontinued, and no benefits were ascribed to the

pregnenolone acetate. No serious side-effects were found in these patients treated with cortisone.

As a result of their experience these authors believe that the use of cortisone in the treatment of atopic dermatitis should be confined to severe cases in which all conventional treatments have failed to arrest the progress of the disease. In these cases the course of therapy should be limited to 4–6 weeks. They also believe that this therapy is contraindicated in mild to moderate cases of atopic dermatitis. They found that:

> the most objectionable feature of cortisone therapy was the development, in almost all instances, of a depressive reaction coincident with relapse. Atopic dermatitis is a chronic illness and patients are usually able to establish a mental adjustment to their condition. Concomitant with the dramatic objective effects of cortisone, our patients obtained an equally dramatic subjective improvement, which engendered the thought that at long last the cure for their terrible affliction was at hand. Unfortunately, with the cessation of therapy they were unable to accept the return of their dermatitis and requested or demanded more cortisone, despite our advice to the contrary. In several individuals these demands were, in many respects, comparable to those seen in drug addicts.

Psoriasis

The much quoted remark that the dermatologist's patients never die and never get well was undoubtedly prompted by the failure of psoriasis to respond to therapy. Most physicians, even dermatologists, take a defeatist attitude toward this disease. It has been my experience that many patients with psoriasis are relieved and stay well, with or without treatment; only a small percentage fail to respond to any therapy. With this in mind, I believe that care should be used in the type of therapy selected. It is, therefore, with misgiving that the treatment of psoriasis with these drugs is even mentioned. I was recently asked at a well known clinic: "What further treatment do you prescribe when you have cleared a psoriatic with cortisone?" I replied that I did not believe cortisone was indicated in the treatment of psoriasis, an opinion I believe to be held by most dermatologists who have observed or treated these patients with this form of medication. Such therapy might, however, be indicated in a very sick patient with an exfoliative dermatitis following an acute or overtreated attack of psoriasis, or in one severely ill with psoriatic arthritis.

Many theories have been offered concerning the etiology of psoriasis, and new ones are constantly being suggested. Charpy[35] postulates that total adrenocortical extracts have in proportion to the doses used a direct and constant favorable action on the eruptions and rheumatism in psoriasis. Doses corresponding to 800 or 1000 gm. of fresh gland daily are required to obtain a bleaching of skin in from fifteen to twenty-five days. The adrenotropic hormone of the hypophysis or ACTH (4 injections of 24 mg. daily) yields analogous results that are complete but transitory. Charpy believes that a disturbance of the hypophysis and the adrenal glands is the underlying endocrine basis of psoriasis, with an inhibition of the protein-sugar function, disorders of pituitary origin playing an accessory role. The eruption takes place secondarily and represents a more or less successful correction of the primary disturbance.

Charpy[36] more recently found ACTH to be ineffective also. The Thorn test indicates that the adrenal function is intact in psoriasis but there is loss of receptivity or of response of the pituitary gland. He further states that the seasonal exacerbations of the skin lesions of psoriasis are preceded by an increase in serum albumin and by hypoglycemia; the cutaneous eruption tends to compensate for these metabolic abnormalities. The treatment of psoriasis should aim to correct these abnormalities of protein and glucose metabolism. The adrenocortical extracts apparently have an effect on such abnormalities. ACTH must be given in large dose.

Thorn and his associates[2] reported definite improvement in 3 cases of psoriasis after thirteen to ninety days of therapy. Two patients with the chronic discoid form of the disease had complete remissions of three months' duration at the time of writing, both receiving 40 mg. of ACTH over a period of nineteen days; three days after treatment was stopped the eruption reappeared. Response to a second and third course of ACTH was less dramatic.

O'Leary's group[37] found that 4 patients with psoriasis and psoriatic arthritis showed prompt response to cortisone therapy, especially in the articular symptoms, the skin responding more slowly. However, when the cortisone therapy was stopped the cutaneous and joint symptoms returned. In 1 of these patients a previously mild psychotic state became pronouncedly aggravated.

Spies and Stone[31] treated 2 cases of typical chronic psoriasis of several years' duration, first with cortisone by injection, 300 mg. initially and 150 mg. daily thereafter for six days, the eruption subsiding by 70 to 90 per cent. Two subsequent courses of cortisone of four and eight weeks, respectively, followed. Within six weeks of the last course of therapy the eruption had recurred in all its original intensity. The 5-mg.-per-gm. cortisone-acetate ointment was applied twice daily to 1 lesion on each patient. After twenty-four days of therapy the lesions were 75 per cent healed.

Another report[4] describes treatment of 3 cases of psoriasis with arthritis, 2 of them with ACTH for two and a half months and six months, respectively; no relapse occurred. The third patient relapsed when the hormone was discontinued. Two cases of psoriasis vulgaris showed no response at all to adequate doses of ACTH.

A patient was presented at a meeting of the Minnesota Dermatologic Society[38] who had been given cortisone from May 21 to July 2. During the first week or so the psoriasis showed moderate im-

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provement and the arthritis was considerably better. Then the lesions began to get worse, and after cortisone was stopped they were more severe than they had been before treatment. ACTH was administered from July 30 through August 26, 80 mg. daily until August 10. Little change was noted in the skin. The dosage was increased to 160 mg. daily, and after thirty-six to forty-eight hours the patient stated that her skin was improved. Improvement continued, the erythema decreased first, the scaling and infiltration subsiding later. By August 27 the lesions were not recognizable as psoriasis. Many areas had cleared altogether except for a residual staining. The arthritic symptoms were also much improved. After the ACTH was discontinued, acneform lesions were noted on the forehead, and hair had increased on the upper lip. During the first week after treatment ended the psoriasis had not recurred, but in the second week (the week previous to presentation) a rapid recurrence of skin lesions on the forearms, legs and scalp was noted.

Of 4 cases reported by Brodthagen and others,[39] only 1 showed temporary improvement. All except 2 showed signs of increased adrenocortical function.

Generalized erythrodermia (generalized desquamation of the skin) is a serious and often fatal disease. Cohen and Distelheim[40] report that this condition resulted after treating a twelve-year-old girl with psoriasis with ACTH, 50 mg. daily for thirty days.

Purpura.

Stefanini and others[41] report a three-year-old boy with a severe purpura, associated arthritis, abdominal pains and red cells, casts and albumin in the urine, who became intolerant to sulfadiazine. The purpura, at first responding to penicillin treatment, recurred, this time apparently refractory to this drug. Aureomycin was administered over a six-day period, with no effect. The patient became worse, developing severe abdominal pain. A fourteen-day course of ACTH therapy was begun; 5 mg. of a special preparation developed at the New England Medical Center was injected subcutaneously three times daily — a total of 210 mg. The purpura subsided in a few days, and the urinary signs improved but did not become normal. The abdominal pains, arthritis and fever subsided rapidly, and by the sixth day the child had recovered. The purpura recurred a month later but cleared in a few days without treatment.

Bullous Eruptions

All bullous eruptions were formerly classified as pemphigus. With increasing knowledge, however, and discovery of some of the etiologic factors, we have been able to place some of these disorders in their proper categories, and we can now differentiate the various types of impetigo contagiosa, the bullous eruption occasionally noted in syphilitic infants, the lesions associated with leprosy, those caused by certain external irritants and sensitizers and the eruptions that follow a fixed pattern, such as the erythema multiforme bullosa type. This last group is often mistaken for pemphigus but is self-limited, whereas the disease called pemphigus vulgaris is invariably fatal, whether acute or chronic. Remissions do occur, nevertheless. The literature of the last twenty-five years contains many reports of "cures," but during my association with a large municipal hospital I have seen many of these "cured" patients finally die of the disease. The alleged cures were apparently the natural remissions that occur in the chronic form of the condition.

Treatment of pemphigus has always been a problem. The advent of these new drugs was therefore heralded as a great boon to its victims. Cannon and his associates[42] summarizing their experience in treating 7 patients with pemphigus vulgaris, state that the therapeutic response to these hormones has been far more impressive than any observed with other forms of treatment. Two of the 7 patients died of fulminating pemphigus, with fever, prostration and, at the inception of treatment, a rapid increase in the number of cutaneous lesions. One showed no response at all to ACTH and probably died of mesenteric thrombosis, possibly induced by the hormone. The other patient responded initially to the hormone but relapsed when the dosage was decreased and failed to respond to increased doses of the compound. The survivors are much improved, but in all cases the disease remains active, and all patients are still receiving treatment. None can be considered cured. In 3 cases some new lesions continue to develop, and unhealed areas from old lesions persist despite continued treatment. When treatment was begun, however, all patients were severely afflicted with rapidly developing lesions. Several had failed to respond to the usual therapeutic measures, including penicillin, aureomycin, Chloromycetin, whole-blood transfusions, liver extract, Naphuride (suramin sodium) and irradiation of the liver and spleen. One patient required 500 mg. of cortisone daily for fifteen days to reach a satisfactory stage of remission. According to these writers' subsequent experience, enormous doses of glucocorticoid compounds may be necessary to control some cases of pemphigus. Cannon concludes that treatment with ACTH or cortisone certainly reduces the burden of managing a patient with pemphigus. Three patients are living at home and able to care for themselves. Two are in general wards without special nurses. The most disturbing feature of this type of therapy has been the fact that it has in most cases been necessary to employ successively larger doses of the hormones in order to keep the disease under control. No difference has been noted between the effects of the two hormones. In sufficient doses both abolished fever and brought about euphoria in twenty-four to forty-eight hours as well as a prompt diminution in vesiculation, no new lesions appearing after about a

week. Old lesions healed slowly after about seven to ten days of therapy.

Combes and Canizares[43] gave cortisone to 6 patients with pemphigus vulgaris. One patient died, 3 showed no improvement (1 developed marked depression) and 2 showed complete and dramatic remissions of three months' duration at the time this report was written and were receiving small maintenance doses. One patient was given ACTH for three days without benefit.

Other writers have reported similar experiences. Brodthagen and others[39] stated that a dramatic remission was observed in 1 patient with pemphigus vegetans who was almost moribund when treatment with pituitary adrenocorticotrophic hormone was started. Three months after treatment was stopped no relapse had occurred. Another patient with pemphigus vulgaris relapsed a few days after pituitary adrenocorticotrophic hormone treatment was discontinued.

O'Leary[37] describes cases of pemphigus vulgaris and pemphigus foliaceus treated with cortisone. In 1 case of early pemphigus foliaceus the lesions involuted completely and remained so for three months. In another patient with pemphigus foliaceus temporary improvement took place twice after a course of cortisone, but during the week of post-cortisone depression blistering and dissolution of the skin recurred in exacerbated form.

Sulzberger and others[4] reported 1 patient with pemphigus vulgaris now on maintenance dosage of ACTH (75 to 100 mg. per day) with no relapse and no toxicity after six months. One patient made no improvement at all and died. Two other patients with pemphigus vulgaris showed moderate improvement but were never completely free of bullae. Both relapsed immediately when treatment was discontinued. One died sixteen days later. In the other, the eruption cleared completely when Naphuride was given in conjunction with cortisone; this patient had responded only moderately to cortisone alone. A fifth patient showed little or no response to ACTH or cortisone. One patient with pemphigus vegetans showed moderate benefit from ACTH, 100 mg. daily for two months. The bullae disappeared, but vegetating lesions remained unchanged. At the time of writing this patient was receiving 100 mg. of cortisone orally per day, with no further change except severe mental depression, moon facies and ankle edema. Two cases of pemphigus foliaceus did not respond to ACTH in 100-mg. doses given daily for twenty-five days.

Thorn and others[2] report that 1 patient with severe vegetative pemphigus who was given 100 to 200 mg. of ACTH for twenty days showed arrest of the eruption and healing of the erosions but died of an overwhelming septicemia.

It seems, therefore, that until a better remedy is found these drugs are well worth a therapeutic trial in a fatal disease such as pemphigus, although conservative dermatologists who have been using them since their introduction have found they have no permanent effect. Rubin[44] reports a patient with pemphigus treated with ACTH who had remained clear of any symptoms for eight months.

Before instituting this therapy, however, one should attempt to establish a definite diagnosis, to avoid using these drugs in more or less self-limited cutaneous eruptions or in eruptions that should respond to less expensive medicine.

A case of Stevens–Johnson syndrome with a severe toxemia, complicated by *Pseudomonas aeruginosa* septicemia, was treated by Yates and his co-workers[45] with cortisone, Chloromycetin and streptomycin. The eruption appeared after a sunburn as a diffuse erythema that faded and was replaced by a maculopapular eruption, soon becoming vesicular and bullous, with hemorrhages and necrosis appearing in the skin. The temperature rose to 105°F. Subsequently there developed a pustular conjunctivitis, severe ulcerative stomatitis and pharyngitis. The serum-electrolyte balance was disturbed and edema appeared. The patient was given cortisone intramuscularly, 50 mg. every eight hours for six doses, 50 mg. daily for two days, 25 mg. daily for two subsequent days and finally 12.5 mg. daily for two days. Dramatic improvement occurred within thirty-six hours. Recurrent temperature elevations took place a few days after the initial improvement and were finally explained when a blood culture showed *Ps. aeruginosa*. The same organism was cultured from a venesection site that had been in continuous use for eight days. The septicemia was controlled by antibiotics and the patient was well on the thirty-sixth hospital day.

Cannon and others[42] report 2 cases of epidermolysis bullosa of the congenital dystrophic type that did not respond to hormone therapy.

Miscellaneous Diseases

Sulzberger and others[4], using these drugs in miscellaneous dermatoses, reported initial improvement in 2 cases of exudative discoid and lichenoid chronic dermatosis, with relapses after discontinuance of ACTH. One case of nummular eczema treated with ACTH showed considerable improvement, and the patient continued to improve on local therapy when the hormone was stopped. A case of Kaposi's hemorrhagic sarcoma failed to respond to ACTH. This drug was also tried in 2 cases of reticulum-cell carcinoma, one of which failed to respond. The other patient improved considerably, with involution of the skin lesions, but developed a toxic psychosis that disappeared when the ACTH was discontinued. The lesions responded to x-ray therapy. Demerol, protamide, aureomycin, snake venom, autoblood and placebos failed to relieve severe pain following a facial herpes zoster. The patient was given 2 injections of ACTH, 25 mg. each at six-hour intervals, and the pain completely

disappeared. Over a period of twenty-eight days the patient was free from pain on 12.5 to 25 mg. of ACTH at eight- to twelve-hour intervals. The pain recurred when the hormone was stopped but was relieved by aspirin. A patient with lichen planus of six months' duration showed initial regression and complete disappearance of the lesions after ten days of ACTH, 75 to 100 mg. daily. The pruritus had subsided in five days. A week after therapy was stopped the lesions and pruritus recurred and cortisone was instituted. Two cases of dermatitis herpetiformis failed to respond to ACTH; a third had complete remission on 100 mg. of ACTH daily.

Treatment of Sjögren's syndrome[46] with adrenocorticotrophic hormone caused the swelling of the lacrimal and salivary glands to disappear; the secretion of saliva and tears reappeared, and the fever and general malaise subsided. This improvement continued for nearly a month after treatment ended, but ultimately a relapse occurred.

Ogryzlo and Graham[47] administered ACTH to 3 patients with clinical symptoms of Reiter's syndrome. Cortisone was given to 1 patient, both intramuscularly and orally. All 3 patients showed prompt and dramatic response. When the hormones were withdrawn relapse occurred, mild in 2 cases and more severe in the third. Two patients recovered after the relapse and are now employed; the third is still under observation. The course of the disease was materially reduced in the 2 patients who recovered and probably in the third also. The writers believe that the improvement in the 2 cases suggests a possible therapeutic application of ACTH and cortisone in a self-limited disease such as Reiter's syndrome.

Five cases of herpes zoster (1 ophthalmic) were treated by Nickel[48] with ACTH. The average dose was 10 to 15 mg. every six hours. All had relief of pain by the time the third injection was received, the relief continuing from two to four months. The skin picture, however, followed its usual course.

Farber and Mandelbaum[49] report a case of erythema nodosum treated with excellent results with a total of 700 mg. of cortisone.

The problem of hormone treatment of cutaneous diseases in pregnant women will probably often arise. I have already been consulted by physicians concerning this. Because the adrenal gland is enlarged in pregnancy, these drugs would not seem to be of value in treating any eruption or toxemia occurring in this condition. According to Robertson,[50] ACTH causes hypertrophy of the adrenal gland and produces its clinical effects by inducing the patient's own adrenal gland to produce cortisone or cortisone-like compounds.

The only report that I can find in the literature is that of Ferguson,[51] who relates his experiences with ACTH and eosinophil counts in normal pregnancy and toxemia. The pronounced metabolic changes reported by others were not found to occur in the pregnant women he treated with ACTH, whether pre-eclampsia was present or not. The ACTH may have been a factor in the cases of the 5 women who went into labor while under treatment. Four of the 9 patients experienced heartburn while receiving ACTH — and only at that time. Ferguson found that usually therapeutic doses of ACTH had no definite effect on pre-eclampsia or normal pregnancy. The failure of the pregnant women to show expected physiologic changes suggests that they may be peculiarly resistant to ACTH.

Sarcoid

Thorn and others[2] found ACTH ineffectual in a patient with uveitis due to sarcoidosis. The adrenal response was poor.

Siltzbach, Posner and Medine[52] report the successful use of intramuscularly administered cortisone in a case of generalized sarcoidosis with extensive and severe bilateral ocular involvement. The patient's vision had deteriorated steadily over a seven-month period in spite of conventional therapy at two ophthalmologic institutions, and when she presented herself for admission to the Montefiore Hospital she was almost blind. From the first day of treatment the patient's vision improved, and when cortisone therapy was discontinued she had 76 per cent normal binocular vision and was able to resume all her usual daily activities.

Randolph and Rollins[33] report 2 patients with sarcoid, both young Negro women. One had a skin eruption of three and a half years' duration, with generalized lymphadenopathy, uveitis, hepatosplenomegaly, impaired adrenal function and hyperglobulinemia. After treatment with cortisone the ciliary injection disappeared in seventy-two hours, with marked involution of the skin lesions. Hepatosplenomegaly remained. X-ray examination revealed marked decrease in the size of the hilar lymph nodes. In the last day of treatment the patient was antagonistic and irritable. Four days later she had an epileptiform convulsion and was committed to a mental hospital, where a diagnosis of paranoid schizophrenia was made. The other patient had generalized lymphadenopathy, cough and generalized pain of three months' duration. The chest film showed hilar widening. Some evidence of impairment of adrenal function was present. Cortisone was given intramuscularly in 100-mg. doses twice daily for nine days, then once daily for two days. Lymph nodes, including the mediastinal nodes, decreased in size in forty-eight hours. At the end of treatment the lacrimal and parotid glands could not be palpated, and x-ray films showed the hilar thickening to have almost completely disappeared. According to these writers, the evaluation of therapy in this disease is difficult because of the frequency of spontaneous remission. Fifty per cent of their previous cases[46] showed marked improvement over an

average interval of five years. However, the marked and swift regression observed in these 2 patients could not be considered coincidental to the cortisone therapy. The greater improvement in the second patient suggests that the drug is more effective in the treatment of relatively acute lesions. The post-treatment psychosis was severe, requiring shock therapy in the first case. The larger dose of the drug could have been responsible, but latent psychotic trends were probably present.

Sulzberger and others[4] report moderate diminution in the induration of Boeck's sarcoid lesions after eleven days' treatment with ACTH.

Lovelock and Stone[53] report preliminary observations on 2 patients treated for sarcoid with cortisone. In both cases significant clearing was shown roentgenographically in six days, and in one case there was almost complete clearing at that time. In this report the writers show that cortisone will produce an unequivocal and pronounced regression of the pulmonary lesions in Boeck's sarcoid. The permanence of these changes is yet to be demonstrated. In the final analysis, they state, the relapse rate and perhaps the toxicity will determine the therapeutic usefulness of cortisone in this disease. They found that cortisone produced no significant toxic effects in these cases.

Lymphomas

The greatest sensitivity to adrenocortical hormones is shown, according to Sprague,[21] by lymphocytes and blood eosinophils, which, he points out, have evolved from the primitive mesenchyme. The effect on these tissues of exogenous cortisone and ACTH has, in his words, "found a limited therapeutic and diagnostic application in clinical medicine."

It is only natural that ACTH and cortisone therapy should be applied to the lymphomas, but the following reports show that in this connection hormone therapy has been of little or no value.

Since Pearson and his co-workers[54] reported a temporary regression of enlarged lymph nodes in chronic lymphatic leukemia and in Hodgkin's disease, Tulipan[55] thought that it would be interesting to observe what effect this substance would have on mycosis fungoides. He began a course of ACTH therapy in 1 such case, administering 25 mg. in 2 cc. of saline solution intramuscularly every six hours, giving a total of 650 mg. over a period of seven days. The pruritus and the infiltration of lesions markedly decreased within two days. Day by day the lesions flattened out, becoming less infiltrated and covered with fine scales. One week after the injections were stopped, however, the pruritus reappeared and the lesions became infiltrated. Since then the lesions have all reappeared in full force, together with a severe pruritus, despite the fact that the patient had for two weeks been receiving a daily maintenance dose of 25 mg. The effect, then, though striking, was only temporary, the rapid improvement observable with 100-mg. daily doses ceasing when the medication was stopped or reduced to 25 mg. per day.

In their experience with ACTH in the treatment of mycosis fungoides, Kierland and others[29] and Sulzberger and his associates[4] found that the drug produced relief from itching, but 1 of Sulzberger's patients, after an initial involution of lesions and relief of pruritus, relapsed one week after ACTH was stopped and failed to respond to a second course of treatment. Sulzberger and his co-workers also report a good initial response in 1 case of Hodgkin's disease of the skin, but new tumors appeared later. There was also good temporary response in a case of leukemia cutis, but relapse occurred in two months, the patient dying subsequently.

So-Called Collagen Diseases

According to Sprague,[21] certain of the derivatives of the primitive mesenchyme, among them connective tissue, synovia, reticulum, vascular tissue and muscle, figure prominently in the so-called collagen diseases. Exogenous cortisone and ACTH can markedly reduce inflammation of these tissues and modify the clinical manifestations in such cases. This therapeutic effect would be more easily understood if we knew more about the mechanism of the action of cortisone and ACTH on mesenchymal tissues, but present-day understanding of this is still incomplete.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38021

PRESENTATION OF CASE

First admission. A fifty-one-year-old woman was admitted to the hospital because of constipation for two years and the sensation of "carrying a load in the stomach" for six months. Physical examination showed a round, firm, movable, nontender mass in the lower abdomen. A total hysterectomy, with bilateral salpingo-oöphorectomy and appendectomy, was performed; the findings were a 10-cm. pseudomucinous cystadenoma of the right ovary, a carcinoid tumor of the appendix that invaded to, but did not penetrate, the serosa, and a few small leiomyomas of the uterus.

Second admission (two years later). Six months before this entry the patient began having episodes of nausea, vomiting, abdominal cramps and diarrhea that occurred at six-week intervals. The most severe episode took place on the day before admission. The nausea and vomiting occurred first and were followed by severe cramps, which began in the epigastrium and encircled the umbilicus; this was usually followed by the passage of loose stools, which were normal in appearance. For about a year the patient had noted "a vague pulling sensation" in the epigastrium. On the morning of admission she passed 3 loose black stools and lost consciousness briefly. There had been no jaundice, fever, hematemesis or radiation of pain to the back; there had been no bloody or tarry stools except for those passed on the day of admission. Eleven months before entry a barium-enema examination showed some redundancy of the large bowel.

On physical examination the heart and lungs were normal. There was no abdominal tenderness and no palpable abdominal masses.

The temperature was 99°F., the pulse 100 and the respirations 20. The blood pressure was 110 systolic, 80 diastolic.

Urinalysis was negative. Examination of the blood showed a hemoglobin of 9.8 gm. and a white-cell count of 8900. A stool gave a +++ guaiac reaction. A gastrointestinal series showed a small hiatus hernia that emptied readily in the upright position. In the superior base of the duodenal cap there was a constant small pooling of barium with minimal radiation of mucosal folds from it. The duodenal cap was somewhat spastic, and there was point tenderness over the area. A cholecystogram was negative.

The patient was given two whole-blood transfusions and was discharged on the sixth hospital day on conservative ulcer therapy.

Final admission (three and a half months later). She had improved somewhat on ulcer therapy; the epigastric "pulling sensation" was somewhat less severe, and the nausea, vomiting and cramps were infrequent for two months. One month prior to entry the abdominal cramps recurred; a gastrointestinal series showed a normal stomach and duodenum, and the jejunum immediately beyond the ligament of Treitz appeared to be encircling a mass about 6 cm. in diameter (Fig. 1). The mucosa over this area was abnormally thickened and almost polypoid. Review of the previous films showed that a smaller mass had been present at that time. There had been no anorexia or weight loss. She had had no further episodes of tarry or bloody stools.

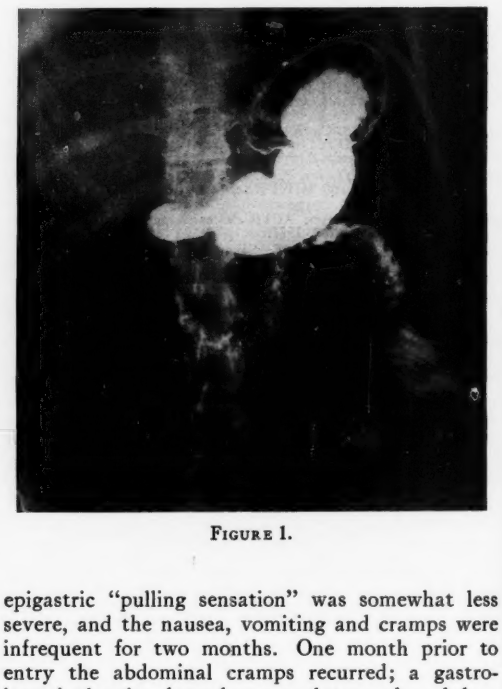

FIGURE 1.

Two months before admission she had an episode of severe crushing anterior-chest pain that radiated around to the back and was associated with dyspnea and perspiration. This had lasted only a few minutes and then subsided completely. She had had a similar short-lasting episode a few weeks before the second admission.

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On physical examination there was a Grade I to II blowing basal systolic murmur. The lungs were clear. The abdomen was relaxed and nontender, with no palpable organs or masses.

The temperature was 98.8°F., the pulse 80 and the respirations 20. The blood pressure was 150 systolic, 100 diastolic.

Examination of the blood showed a hemoglobin of 12.4 gm. and a white-cell count of 8100. Two stools were guaiac negative. An electrocardiogram showed a normal rhythm at 85, with a PR interval of 0.17 second, a QRS interval of 0.08 second and a normal axis. The T waves were low upright in Leads 1, 2, V_1 and V_2 and flat in Leads 3, AVL, AVF, V_3, V_4, V_5 and V_6; they were somewhat lower than on a previous tracing. A roentgenogram of the chest showed elevation of the right leaf of the diaphragm.

On the fourth day an operation was performed.

Differential Diagnosis

Dr. John W. Raker*: Two years before her last admission this fifty-one-year-old woman had a proved pseudomucinous cystadenoma of the ovary, which apparently was a benign lesion as far as the pathologist could tell. She also had an incidental carcinoid tumor of the appendix that had not perforated the serosa of the appendix. The appendix was probably removed as a routine part of the operation. Two years after that she was readmitted with symptoms that were largely gastrointestinal in nature. She had epigastric pain and at least one episode of severe gastrointestinal bleeding. The bleeding was thought to have come from a duodenal ulcer; perhaps Dr. Wyman can prove that a duodenal ulcer was present. At any rate, it was questionable whether an ulcer actually was the lesion that was bleeding, as on a repeated x-ray examination three and a half months later a mass was found in the region of the upper jejunum; on review of the previous x-ray films the same mass was noted. Her symptoms had persisted after the bleeding stopped. Therefore, one wonders whether she had a duodenal ulcer at all.

One additional diagnosis is practically given to me. The patient had an episode of crushing anterior-chest pain radiating to the back associated with dyspnea, perspiration and, apparently, changes in the T waves in the electrocardiogram that I think are consistent with damage to the coronary artery. I am going to assume that this patient had probably had an old myocardial infarction or at least some coronary-artery disease. There are other possibilities, but a differentiation among them all cannot be made on the evidence I am given.

I have to decide on the nature of the upper-jejunal mass. I shall make my diagnosis and see if Dr. Wyman will change it. It seems to me that this is really a case in which the diagnosis should be made from the x-ray films. The description given here is that of a large mass 6 cm. in diameter just beyond the ligament of Treitz, where the jejunum was encircling the mass. The mucosa was abnormal — much thickened and almost polypoid. The episodes that the patient had suggest a moderately severe intermittent intestinal obstruction. The real question is: Was this mass extrinsic or intrinsic to the small bowel? I am not sure that I can determine that from the evidence at hand. I suppose a carcinoid could present this picture. It would be unusual to find only one mass; it would also be unusual for a carcinoid to metastasize from a tumor that had not perforated the serosa of the appendix. I would also be inclined to rule out a metastasis from the cystadenoma of the ovary. Pseudomucinous cystadenomas are likely to be less malignant than the other types; furthermore, there would probably have been more evidence of generalized abdominal involvement — and perhaps ascites as well. I shall exclude an extrinsic mass of the jejunum.

If the mass was intrinsic to the jejunum, it could be arising in the wall or it could be a tumor or an inflammatory process arising in the mucosa. I do not know that I can determine which was the site of origin. I am going to assume for the purpose of this discussion that the bleeding came from this mass in the jejunum and not from a duodenal ulcer, and that it probably indicates that an area in the jejunal mucosa was ulcerated. I cannot exclude a lesion of the spindle-cell variety like a leiomyoma that might have arisen in the small-bowel musculature and ulcerated by pressure through the overlying mucosa, but I shall make a diagnosis of primary disease of the mucous membrane, such as lymphoma in the upper region of the small bowel. I shall rule out an inflammatory process on the basis of two things: First, the disease seems to have been localized in an unusual area of small bowel for an inflammatory process, and secondly, the history of gradual progression without much remission is in favor of tumor rather than of an inflammatory process. I shall make my first choice lymphoma or a tumor primarily involving the mucosa of small bowel and my second choice a tumor of the small-bowel wall involving the mucosa secondarily, such as a leiomyoma or something similar. Dr. Wyman's interpretation of the x-ray films may make me change the order of my choices.

Dr. Stanley M. Wyman: I think you can all readily see this distinct rounded mass encircled by the distal duodenum and the proximal jejunum (Fig. 1). This is a constant finding in all the films. It was followed for three and a half months. The question about the abnormal duodenal cap I cannot answer with certainty, but I believe the radiologist who saw this patient finally decided that the duodenal cap was normal. This mass seems to be as

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nearly round as one can expect to find it. The mucosa over it seems to be thickened; the folds seem prominent, but there seems to be no frank ulceration that I can be sure of; there does seem to be some irregularity of the superior aspect of the jejunal mucosa at this point. I should think that this mass was intimately adherent to the wall of the jejunum, perhaps arising in it. I do not think that I would put lymphoma first; I would make spindle-cell tumor my first thought.

DR. RAKER: I would have to be governed by the wisdom of the radiologists and agree that the mucosa looks as though it were not involved extensively and that probably a tumor of the wall of the small intestine would be more likely.

DR. BENJAMIN CASTLEMAN: Dr. Ingelfinger, have you any comment?

DR. FRANZ INGELFINGER: Lymphoma would not usually have such a sharply circumscribed area when it involved the intestine; it would go through the intestinal wall rather than involve one side of it. The mass apparently has not changed much in size during the three and a half months, and the mucosal folds do not seem grossly involved. I would favor a more benign sort of tumor arising close to the jejunum.

DR. CHESTER M. JONES: Aren't ulceration and bleeding more likely with a spindle-cell tumor than with a lymphoma?

DR. CASTLEMAN: No; ulceration is very common in a lymphoma. The ulceration from an intramural extramucosal tumor is usually small — not so large as with lymphoma.

Could you rule out a large mesenteric node pressing against the bowel, Dr. Wyman?

DR. WYMAN: A node in the root of the mesentery would produce this type of pressure defect on the bowel only if it had grown sufficiently to be close to the wall of the bowel.

DR. INGELFINGER: A mesenteric cyst could produce a picture similar to that.

DR. RAKER: Yes; but the gastrointestinal bleeding would be unlikely.

CLINICAL DIAGNOSIS

Tumor of jejunum.

DR. RAKER'S DIAGNOSIS

Spindle-cell tumor of jejunum.

ANATOMICAL DIAGNOSIS

Leiomyoma of jejunum.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This patient was operated on by Dr. Joe V. Meigs, as he had previously removed the ovarian tumor. When he saw this tumor at operation he thought seriously of a metastasis from the carcinoid. I do not believe I have ever seen a metastasis from a carcinoid of the appendix. When metastatic carcinoid occurs, it is from a primary lesion in the intestine, usually the ileum. This photograph shows the external view of the tumor within the mesentery close to the bowel wall (Fig. 2). When the bowel was opened the tumor proved to be an intramural, extramucosal tumor with ulceration (Fig. 3); on microscopical examination this proved to be a benign leiomyoma.

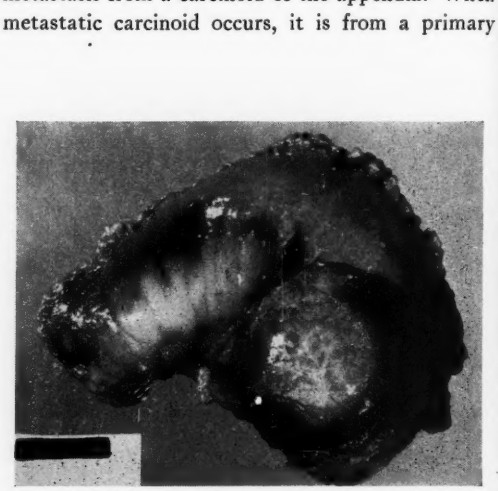

FIGURE 2.

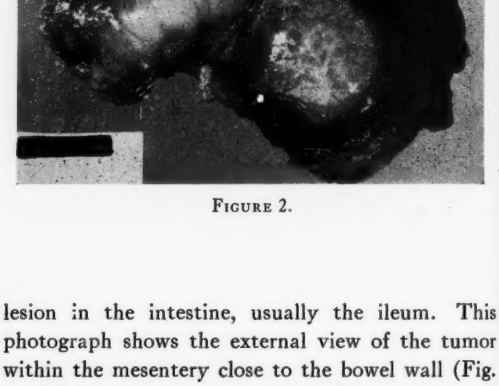

FIGURE 3. *Jejunum. Arrow points to lesion.*

CASE 38022

Presentation of Case

A fifty-seven-year-old man was admitted to the hospital because of hematuria.

Fifteen years before admission the patient had had transient right-flank pain and hematuria for a period of two days. Similar attacks occurred five years and ten days prior to admission. For the three days before entry the patient passed bloody urine containing clots; the blood persisted throughout urination. There was no pain. He had no chills, fever, frequency or urgency.

At eighteen years of age he had a massive pulmonary hemorrhage. He was treated at home by bed rest. He did not have night sweats, cough or chest pain. There had been no further hemoptysis. At thirty-one years of age he developed an eruption of secondary syphilis and was treated with arsenic and bismuth.

On physical examination the lungs, heart and abdomen were normal. The prostate was twice normal size and was irregular and hard. There were a number of hard nontender 1-cm. nodules in the head and body of both epididymides. The testes were definitely larger than normal and felt heavy.

The temperature was 99.8°F., the pulse 96 and the respirations 20. The blood pressure was 180 systolic, 85 diastolic.

The urine was cloudy red, had a specific gravity of 1.022 and gave a +++ reaction for albumin; the sediment contained 100 red cells and 15 white cells per high-power field. Examination of the blood showed a white-cell count of 19,500 and a hemoglobin of 14.2 gm. The nonprotein nitrogen was 26 mg. per 100 cc. Roentgenograms of the chest showed scattered calcified scars in the right upper lung and right paratracheal region, with several small calcifications in the left midlung. The heart was not enlarged. An intravenous pyelogram showed the kidneys to be normal in size, shape and position. The right kidney showed normal function and structure. On the left the excretion was slow, and visualization of the calyces was incomplete even at 30 minutes. In the visualized calyces the contour was irregular, and the superior minor calyx was enlarged. Cystoscopy showed a normal bladder. The urine from the left ureter was bloody; a gram-stained smear of this showed no organisms, and there was no growth on culture. A left retrograde pyelogram showed irregularity of all the minor calyces (Fig. 1). These were larger in size than normal, and the inferior calyces had rather narrow infundibula. There were a number of radiolucent areas in the renal pelvis.

The patient continued to pass grossly bloody urine. On the third day an operation was performed.

Differential Diagnosis

Dr. Lorande M. Woodruff*: May I see the x-ray films?

Dr. Stanley M. Wyman: The old calcifications and fibrotic scarring in the right upper lobe are clearly visible and are consistent with an old tuberculous infection. The kidneys are fairly well outlined; the right certainly appears normal in size and shape. The left is a little harder to visualize well; it is probably not too unusual in contour. There is delay in excretion of the intravenous contrast substance by the left kidney; when it is visualized there seems to be a widened upper calyx and a rather wide pelvis with some irregular rarefaction in its center. The other calyces are very poorly visualized. The films taken from the retrograde examination demonstrate rather well the blunted, irregular minor calyces with rather pinched, narrowed infundibula (Fig. 1). There seems to be some non-

Figure 1.

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opaque filling defect in at least one calyx and in the region of the kidney pelvis.

DR. WOODRUFF: How well can you define the size of the left kidney?

DR. WYMAN: I cannot define it at all well. I have the impression that at least the lateral aspect is narrowed to a considerable degree. I think it is somewhat shrunken.

DR. WOODRUFF: This fifty-seven-year-old man was admitted with hematuria, which is an acute symptom. Also he obviously had a chronic condition, because he had had bleeding fifteen and five years before admission. In general this was painless, but fifteen years before entry he had transient right-flank pain associated with the hematuria. The pain was not definite enough to make me think he had been passing a stone; it might well be explained by small blood clots passing down the ureter. Since in the x-ray films the disease seems confined to the left kidney, I wonder if the patient did not confuse the sides during the period of fifteen years. In the last attack he had no fever, chills, urgency or frequency. These four negative findings practically exclude infection in the lower urinary tract as the cause of the trouble. The fact that he had no chills and fever indicates that there was not much pyelonephritis.

The massive pulmonary hemorrhage at eighteen years of age is consistent with tuberculosis, and this is borne out by the later scars in the lungs. The patient was treated at home on bed rest; I cannot be sure how adequately he was treated, but he had no further hemoptysis. At thirty-one years of age he had secondary syphilis, which was treated with arsenic and bismuth. Again, I do not know how adequately he was treated. Thus, in one paragraph of the history we have evidence of the two most common infectious granulomas, either one of which may persist if not well treated.

On physical examination the prostate was enlarged, irregular and hard, which makes me think immediately of carcinoma. One other condition that is difficult to differentiate from carcinoma by palpation is tuberculosis of the prostate. A nonspecific prostatitis would not be as firm as this was. There were a number of hard, nontender 1-cm. nodes in the head and body of each epididymis. Tumors of the epididymis are extremely rare and are not bilateral; therefore these nodules must have been inflammatory — the result of either a bilateral burned-out acute epididymitis or, more likely, a tuberculous epididymitis. There was no mention of how the vas deferens felt. Usually with tuberculous epididymitis there is a vasitis as well, with beading of the cord. The testes were larger than normal and felt heavy. In tuberculosis the testes are usually not involved, and from this description I do not think there was much wrong with them.

On laboratory examination the urine was cloudy and red, with a specific gravity of 1.022. This latter confirms the fairly good renal function demonstrated in the intravenous pyelogram. Possibly the globin from the hemoglobin accounts for the positive albumin reaction, unless the test was done on the supernatant of a centrifuged specimen. In tuberculous renal disease albuminuria is a very common finding. The sediment contained 100 red cells and 15 white cells, showing pyuria in addition to hematuria. The white-cell count of 19,000 is a little difficult to explain, unless the patient had some acute infection along with a chronic process. The normal hemoglobin showed that he was not greatly debilitated by his illness. The x-ray film of the chest demonstrated scars consistent with tuberculosis. According to the report of the intravenous pyelogram, the kidneys were normal in size and shape; I cannot agree that the left kidney was normal in size. Cystoscopy showed a normal bladder, but urine coming from the left ureter was bloody. This is definite evidence that the blood must have come from the left side, and since there is no evidence of obstruction of the ureter the bleeding presumably came from the left kidney.

The differential diagnosis, then, consists of the causes of renal bleeding. Carcinoma is the most important cause. With a hypernephroma, which is the most common tumor, I would expect to find a mass and also some enlargement of one part of the kidney rather than a general distortion, as was present in this case. A papillary tumor of the renal pelvis could cause a filling defect similar to that seen in the pyelogram. If this was the diagnosis I would look for seeding of the tumor along the ureter or in the bladder. These were not present. I would also expect more signs of obstruction. An epidermoid carcinoma of the renal pelvis also could cause such defects in this area; they are prone to bleed very early and to produce some obstruction and may give few other symptoms. However, in this case there is not much evidence of obstruc-

tion. Varices and hemangiomas characteristically give a fairly normal pyelogram and can, I think, be excluded. There was no evidence of calculous disease unless the radiolucent areas described represent nonopaque calculi. From their position, I am sure that if they were stones they would have produced more pain.

That brings me to consideration of tuberculosis of the kidney. This condition starts with tubercles throughout the parenchyma of the kidney, which gradually enlarges. The tubercles rupture into a calyx and thus cause extensive distortion. Also, the associated scarring usually leads to constriction of the infundibulum and further dilatation of the calyces. This is much the picture presented here. Usually with generalized tuberculosis of the kidneys there is considerable ureteritis. What I can see of this ureter looks very smooth, and I see no evidence of any stricture formation. However, I think tuberculosis explains this whole picture better than anything else. The hard nodules in the prostate I can call tubercles. Since they are usually secondary to renal tuberculosis, this is further corroborative evidence. Tuberculosis of the epididymis is also usually secondary to tuberculosis in the prostate; thus these three findings would piece together. My diagnosis, therefore, is tuberculosis of the kidney, prostate and epididymis.

Dr. Benjamin Castleman: Isn't it rare to see a clear bladder in tuberculosis?

Dr. Woodruff: That is somewhat unusual; many who do not have much cystitis have some dysuria and frequency. The complete absence of these symptoms concerned me a great deal. However, some patients with renal tuberculosis have no bladder symptoms and have a normal bladder.

Clinical Diagnosis

Papillary tumor of renal pelvis.

Dr. Woodruff's Diagnosis

Tuberculosis of the left kidney, prostate and epididymides.

Anatomical Diagnosis

Tuberculosis of left kidney.

Pathological Discussion

Dr. Castleman: The surgeon who operated on this patient called this tuberculosis until he saw the retrograde film; then he was somewhat doubtful about what it was; he favored papillary tumor of the renal pelvis. At operation he removed a small kidney weighing only 90 gm. We found in the upper pole of the kidney, in the medulla and inner portions of the cortex, a cavity about 6 cm. in diameter that was filled with caseous material. Also, there were two smaller similar caseous abscesses in the lower pole. These had eroded the tips of the papillae in places and there were some ulcerations in the calyces themselves. Sections showed convincing evidence of tuberculosis.

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NATIONAL HEALTH COMMISSION

THE President of the United States has, at year's end, created a fifteen-member commission "to determine, within the year, the nation's 'total health requirements' and to recommend ways for meeting those needs in both the immediate and distant future."

Although the compass of a twelve-month period may set too sharp a limit on such a vast undertaking, much of the material must be available and ready for evaluation; in any event a plan like this, sincerely conceived and properly executed, merits the most respectful consideration, as should any plan designed to improve the nation's health. The value of any such enterprise must obviously depend first on the sincerity with which it is proposed, — and this should be above question, — then on the character of the personnel selected to carry it out and finally on the acceptance and implementation of its recommendations.

The President has made an excellent choice, as chairman of the group, of Dr. Paul B. Magnuson, who was last year ousted with honor from the medical directorship of the Veterans Administration. Further indications of the judicial character that this committee is intended to assume are the appointment to it of representatives of the American Medical Association, of educational and research institutions and of farm, labor and consumer organizations "to co-operate in the preparation of reports and recommendations."

There is no question, in a democracy such as this, of the freedom of any body of investigators to pursue the truth and to present it honestly. What is more difficult to guarantee is the acceptance of its recommendations, and their execution. Much good might have come from a greater effort to have the recommendations of the Hoover Commission accepted and acted on.

It must be taken with fortitude, however, that the mills of the gods grind slowly, and the truths that are revealed today may not find more than a minority acceptance until tomorrow. For even pigeonholed studies, if they contain revelations that mankind needs, may sometimes break from their encystment and come to active life.

It can be accepted as a foregone conclusion that a commission selected with the earnest intention of furthering the nation's welfare will recommend what it considers to be best in the long run for the nation's good. It must be apparent that such a group of men will have in mind the mistakes made by well-intentioned governments in the past, of which history has record, and will give proper weight in the balance of its judgment to the President's statement calling attention to the health progress made through "federal aid for hospital construction, medical research, and maternal, child health and crippled children's services, and to the efforts being made as well by the several health agencies of the federal agencies and armed services."

It is to be expected that the commission will also take into consideration the progress that medicine has made in this country under the system of free

enterprise that has been found so far to be more effective than any other system that has been devised, and will consider as well the continuing efforts that are being made under this same system.

Mr. Truman's statement that in view of the present world crisis it is particularly important that the drain on the nation's strength through illness and death should be limited need not be regarded as calling attention to a matter that is in itself critically urgent. The health of the nation is constantly improving, and the mortal stroke of death, which comes once to each, has been more and more delayed, with or without federal intervention.

The appointment of a well balanced, unprejudiced commission to study the health needs of the nation is a logical way of bringing further emphasis to bear on the problem. The President is to be congratulated on his determination to seek expert advice, and he should receive the fullest co-operation from organized medicine.

ROENTGENOLOGIC IDENTIFICATION OF BODIES

THE technic of positive identification of persons living and dead has developed apace with fingerprinting and the scientific methods of our authorities in legal medicine. The roentgen survey method has been used occasionally in isolated cases but never with multiple casualties such as occurred in the *Noronic* disaster. Dr. A. C. Singleton reports, in the September, 1951, issue of *Radiology*, on the usefulness of this method, which, without raising any scareheads, may chart the course to be followed in future holocausts.

At 2:30 a.m. on September 17, 1949, fire broke out on the Great Lakes liner *Noronic*. In a few minutes of flaming inferno 119 of her 527 passengers lost their lives. Identification of the bodies was made difficult because of the terrible destruction and distortion of the victims' remains, well attested to by the author's photographs. Extremities and angles of the bodies were either burned away or so charred that fingerprints and other identifying marks were nonexistent. Also, the fire having occurred at night, identifying clothing, jewelry and dentures had been removed.

Since both the legal implications of the identification of a body and the sentimental importance to relatives are great, the attorney general of Ontario requested roentgenologic examination of the unknown victims, and particular attention was given to a comparison of these examinations with those of the victim taken prior to death, which were efficiently collected by the Red Cross.

With three mobile x-ray units set up in a temporary morgue, Dr. Singleton and his staff surveyed 78 bodies (27 male and 51 female) in forty-eight hours. The preliminary survey consisted of anteroposterior projections of the trunk and anteroposterior and lateral projections of the skull and any remaining extremities. As the outside films arrived it was necessary to return to the macabre job of producing films in comparable projections. One thousand and twenty x-ray films were used — an average of 13 per specimen. It required three weeks' continuous work; the last examination was finished ten weeks after the disaster. The pathologists aided greatly in making up exclusion lists from the other pertinent data.

Old fractures or infections were of little importance, but congenital bone anomalies were of considerable value in the identification process. Identification, according to the report, consisted largely of accurate matching of normal bony structures, particularly at the margins of joints. The portions of the body yielding positive identification were as follows: skull, 4; cervical spine, 2; thoracic spine and chest, 13; lumbar spine and pelvis, 9; foot and ankle, 1. Of 35 persons of whom films had previously been taken, 24 were positively identified. In 5, identity was suggestive. X-ray films were also of assistance in cases in which identity suggested by other means was excluded by incompatible roentgenologic comparison. In 6 cases matching was impossible, because of gross destruction of the parts or poor quality of the previously made films.

Comparing these statistics, only 38 of all the victims were suitable for fingerprint study. Of 15 who were fingerprinted 6 were positively identified, and in 9 cases contributing evidence was obtained.

The author's conclusions are well worth considering:

The comparison of roentgenograms made during life with postmortem roentgenograms is a feasible method of body identification. Its success depends upon obtaining satisfactory antemortem roentgenograms of the body to be identified. The identifying points of bones are permanent and are not subject to easy destruction. Where positive, the identification warrants being considered as a definite and final means of proof of death and identification of the body.

Since, in this and other types of disaster, roentgen identification will prove of much greater value than fingerprint identification, the author therefore suggests a longer period of preservation of all x-ray films than is current practice, or microfilming them for permanent record.

ETIOLOGY OF MEGALOURETERS

There appears elsewhere in this issue of the *Journal* an article entitled "A New Concept of the Etiology of Megaloureters," the authors' interest in this subject having been stimulated by their previous work on the etiology, pathology and treatment of Hirschsprung's disease. Earlier observers have also suggested the possibility that these two conditions might have a common etiologic factor, the late Dr. James S. Stone having speculated many years ago on the possibility of the two conditions' being analogous, although his ideas never appeared in published accounts.

It has remained for Swenson and his co-workers, after their careful and painstaking studies, to demonstrate that this supposition may indeed be a valid one. They suggest that megaloureters of the type under discussion are the result of a malfunctioning bladder and that the disturbance of bladder function in such cases is caused by a diminution in the parasympathetic ganglion cells in the bladder wall. There is much yet to be learned, but it seems that the approach to the treatment both of Hirschsprung's disease and of megaloureters of a type that until now has had an unexplained etiology may be on a sounder basis.

THE MILLIONTH VICTIM

On December 22, 1951, the shortest and the darkest day of the year, there occurred at approximately noon the millionth motor-vehicle fatality that has taken place in the United States since the first of these Juggernauts of modern days was constructed with such eagerness. It is a somewhat tragic triumph of the science of statistical prophecy that this epic sacrifice could have been so predicted with nearly the accuracy that pertains to an eclipse, to the day and almost to the hour and minute.

As the years have rolled on, modern man has added to the nonchalance with which he regards the astronomical figures of time and space a certain indifference also to the figures that relate more closely to his own travels through life. The figures that relate to the world's population in point of numbers have become astronomical, and so have the figures that tally up the worldly affairs of men.

Billions of dollars have become a matter of contempt almost as much as of awe; modern armies that are numbered in the millions are capable of inflicting and sustaining losses of life that run also into the millions.

But in another sense the unnecessary loss of even a single life can never be accepted as a mere statistical digit. Regardless of how small a fraction of the whole this phenomenon may appear to be, it represents to the individual, no less than at any time in the history of man, the complete sacrifice of everything on which his worldly aspirations have been centered.

The millionth victim of a type of fatal accident can be dramatized merely as an arithmetic symbol, like the millionth displaced person to enter the country, or the millionth commuter to pass the turnstile of a new subway, and still be but a millionth part of a whole. But to each as an individual the loss is the whole and represents an event that cannot be diluted with numbers. This cannot be lost sight of in those countries where social consciousness has been encouraged to develop.

Some extra copies of the interesting report of the Committee on Obstetrics, to the American Medical Association, in May last, have been worked off. The pamphlet is neatly printed, and is presented in a convenient form for those who may not have access to the large volume which embraces the entire transactions of that learned body for 1851.

Boston M. & S. J., *January 14, 1852*

JAN 23 1952 MANHATTAN KANSAS SCIENCE

MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council of the Massachusetts Medical Society will be held in John Ware Hall, 8 Fenway, Boston, on Wednesday, February 6, 1952, at 10:30 a.m.

Business:

Call to order at 10:30 a.m.

Presentation of record of meeting held October 3, 1951, as published in Supplement No. 1, December 6, 1951.

Reports of standing and special committees.

Such other business as may legally come before this meeting.

H. QUIMBY GALLUPE, M.D., *Secretary*

CORRESPONDENCE

CRITICISM OF AN EDITORIAL

To the Editor: I hope you will find the opportunity to rewrite the editorial "Stark Unreality," for as it is published in the November 15 issue of the *Journal* it is in poor taste.

Unquestionably, "psychosomatic" technics have been overpopularized, misused and abused. This appears to be the fate of every new technic introduced in medicine — for example, vitamins, hormones, antibiotics and others. It seems that a period of time must pass before the flush of enthusiasm abates and each technic takes its proper place among therapeutic agents. As is usually the case with new technics, the abuse and overpopularization of "psychosomatics" is carried on largely by the naïve and uninformed. Uninformed opinion oscillates between overenthusiasm and complete rejection and ridicule. "Stark Unreality" is an example of rejection and ridicule.

The abuse of "psychosomatics" does not detract from the value of the subject any more than the "shotgun" prescription of vitamins detracts from the monumental research discoveries and understanding that in thirty years have eradicated pellagra.

JOHN A. RITCHIE, M.D.

Greenville, South Carolina

To the Editor: The editorial that appeared in the *Journal* of November 15 entitled "Stark Unreality" contains so many sweeping generalizations and irrelevant remarks that it cannot go unchallenged.

The editorial makes a plea for moderation and critical judgment and deplores the "all-or-none principle" after it has indiscriminately lumped all the men working in this field into the straw man called "psychosomaticist." The editorial gives no hint that there is much disagreement among workers in this field concerning fundamental and theoretical concepts, and it implies that all psychosomaticists are uncritical and overly enthusiastic.

With shameful irrelevance, the editorial implies that psychosomaticists are so gullible that their theories are equivalent to "reports of walking through a table instead of walking around it, jumping over it, crawling under it or moving the table itself to get on the other side." This juxtaposition of patent absurdities with a discussion of psychosomatic medicine betrays a biased and even deliberate attempt to ridicule a subject that deserves careful and thoughtful consideration.

I fail to see the pertinence of the remarks concerning proneness to accidents and public safety laws. Again it seems that the writer of the editorial was deliberately trying to make the subject ridiculous. And I do not know of anything in psychosomatic theory or practice that denies the existence of amebic dysenterv.

When the editorial sweepingly condemns the idea that emotions can produce what it terms "disease that has previously been classified as predominantly of organic or exogenous origin" I wonder if its author really conceives of disease processes as dynamic. Has he investigated the evidence that shows quite distinctly that emotional disturbances, either spontaneous or induced, are associated with repeated and profound changes in body function manifested by alterations in electroencephalograms, electrocardiograms, bronchospirometry tracings, gastrointestinal secretion and motility, adrenal-cortical hormone production, cardiac output, blood pressure, renal blood flow, cerebral blood flow, oxygen uptake and skin temperature and blood flow, as well as a host of others? Does he know of the work that has demonstrated that emotional states markedly influence the ability to learn and to develop conditioned reflexes and that they can modify specific neurophysiologic functions such as pain perception and distort specific pharmacologic effects of drugs?

Psychosomatic medicine implies a concept of man that is in keeping with a vast body of empirical and experimental data. It is inconsistent with psychosomatic concepts to overemphasize the "emotional" or underemphasize the "physical." We are striving to develop a viewpoint of man as a total organism in which emotions and feelings are just as real as his bones; it is doing a grave disservice to medical progress to ridicule such attempts — either openly or by holding the entire field of workers and theory responsible for extreme viewpoints and ignorant misconceptions.

SAMUEL B. GUZE, M.D.

St. Louis, Missouri

Note: To point out that excesses and overenthusiasm exist as part of the development of some medical specialty hardly seems to be ridiculous or to constitute rejection. Anyone who has followed the course of psychosomatic medicine should know that unsubstantiated claims have been made and that too often for critical acceptance theories have been pronounced as facts. It does not seem evidence of poor taste to suggest that physicians should not allow their particular professional interests to override their objective judgment. The strength of the medical profession is not lessened by an earnest desire to examine abuses for which it may be responsible.

The editors of the *Journal* agree entirely that it should be "inconsistent with psychosomatic concepts to overemphasize the 'emotional' or underemphasize the 'physical'."

The writers of these letters, in their unquestionably earnest interest in mind-body relations, are perhaps underestimating the trend emphasized in the editorial in question. In spite of a restrained and inquiring attitude on the part of some workers, the dominant tendency in psychosomatic medicine is an overplaying of psychologic concepts, — largely psychoanalytic, — that have no basis in established fact. — ED.

BOOK REVIEW

Functional Anatomy of the Limbs and Back: A text for students of physical therapy and others interested in the locomotor apparatus. By W. Henry Hollinshead, Ph.D. 8°, cloth, 341 pp., with 122 illustrations. Philadelphia: W. B. Saunders Company, 1951. $6.00.

This book on functional anatomy was written especially for young physicians and nurses who were doing postgraduate work at the Mayo Clinic. Since it contains only 341 pages it does not discuss anatomy in detail. After a short review of the various tissues and their purposes, the various organic systems are discussed. The anatomy of the back and limbs is emphasized. Function of muscular groups, particularly in action patterns, is described. The musculature is discussed in the conventional order. There are no anatomic plates, but there are many graphic sketches showing the action of muscles. This is a helpful review book — adequate, but not too long. It should be most helpful to those who require a concise summary of functional anatomy.

JOHN G. KUHNS, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Anatomy in Surgery. By Philip Thorek, M.D., assistant clinical professor of surgery, University of Illinois College of Medicine, associate professor of topographic anatomy and clinical surgery, Cook County Graduate School of Medicine, cosurgeon-in-chief, American Hospital, associate attending surgeon, Cook County Hospital, and senior attending surgeon, Alexian Brothers' Hospital. 4°, cloth, 970 pp., with 720 illustrations. Philadelphia: J. B. Lippincott Company, 1951. $22.50.

This new textbook on surgical anatomy has been developed by the author over a period of twelve years. Strong emphasis has been placed on the surgical point of view, and the well-known "head-to-foot" classification has been used in arranging the material. The illustrations are excellent, the type is good and the publishing is well done. An index of 54 pages concludes the volume.

Practical Clinical Psychiatry. By Edward A. Strecker, Sc.D., Litt.D., LL.D., M.D., professor of psychiatry, University of Pennsylvania School of Medicine; Franklin G. Ebaugh, M.D., professor of psychiatry, University of Colorado School of Medicine, and director, Colorado Psychopathic Hospital; and Jack R. Ewalt, M.D., professor of neuropsychiatry and administrator of hospitals, University of Texas Medical Branch. With a section on *Psychopathologic Problems of Childhood* by Leo Kanner, M.D., associate professor of psychiatry, Johns Hopkins University School of Medicine. Seventh edition. 8°, cloth, 506 pp., with 35 illustrations and 14 tables. New York: The Blakiston Company, 1951. $7.00.

The sixth edition of this textbook was published in 1947. The text has been brought up to date and new material has been added, including a new chapter on general or "support" therapy. Likewise, new material has been added on technics that may be used by the general practitioner in treating psychoneurotics and patients with psychosomatic conditions. The book is well published, and there is a good index. It is a recognized textbook on the subject, as is attested by the publication of 7 editions in twenty-five years.

Lehrbuch der analytischen Psychotherapie. By Dr. Med. Harald Schultz-Hencke. 8°, cloth, 340 pp., with 2 tables. Stuttgart: Georg Thieme, 1951. DM 27. Distributed by Grune and Stratton, New York.

The main body of the text is divided into two large sections: one on the theory of the neuroses, the other on the theory of the analytical procedures of the so-called technic. The book is well published and it has an index of authors and an extensive index of subjects. It should be in all collections on the subject.

NOTICES

SYMPOSIUM ON INFANT FEEDING

The fourth Wednesday evening postgraduate seminar of the series conducted by the Children's Medical Service of the Massachusetts General Hospital will be held on January 16 at 7:15 p.m. in the White 3a Amphitheatre of Massachusetts General Hospital.

The seminar will consist of a symposium on infant feeding. Physicians and medical students are invited to attend.

HAMPDEN DISTRICT MEDICAL SOCIETY

A meeting of the Hampden District Medical Society will be held on January 22 at 6 p.m. at the Hotel Kimball, Springfield. The Hon. Harold Putnam will speak on the proposed establishment of a medical school at the University of Massachusetts.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 11, 21 AND 28. Anesthesia Teaching Conferences. Page 1031, issue of December 27.

JANUARY 12–30. Springfield Hospital. Page 1032, issue of December 27.

JANUARY 14–19. School of Cytology. Page 956, issue of December 13.

JANUARY 15. Harvard Medical Society. Page 40, issue of January 3.

JANUARY 15–31. Boston City Hospital House Officers' Association. Page 1032, issue of December 27.

JANUARY 16. Greater Boston Medical Society. Page 40, issue of January 3.

JANUARY 16. Symposium on Infant Feeding. Notice above.

JANUARY 16. New England Society of Physical Medicine. Hotel Kenmore. 8:00 p.m. Speaker: Dr. Thomas L. DeLorme.

JANUARY 17. Boston Gastroenterological Society. Page 996, issue of December 20.

JANUARY 22, FEBRUARY 26, MARCH 25 AND APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.

JANUARY 23. New England Conference on Allergy and Related Subjects. Page 996, issue of December 20.

JANUARY 23. Suffolk District Medical Society. Page 669, issue of October 25.

FEBRUARY 2, MARCH 1, APRIL 5 AND MAY 3. New England Society of Anesthesiologists. Post-Graduate Education Course. Page 966, issue of December 20.

FEBRUARY 14. Cancer of the Breast. Dr. Ernest M. Daland. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

FEBRUARY 25 AND APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

MARCH 10–13. New Orleans Graduate Medical Assembly. Page 956, issue of December 13.

MARCH 12. Northeastern New York Radiological Society. University Club, Albany, New York.

MARCH 31–APRIL 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

MAY 1–3. American Goiter Association. St. Louis, Missouri.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 7–12. International Diabetes Federation. Page 996, issue of December 20.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Page 916, issue of December 6.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies, Mount Washington Hotel, Bretton Woods, New Hampshire.

DISTRICT MEDICAL SOCIETIES

HAMPDEN

JANUARY 22. Hotel Kimball, Springfield.

HAMPSHIRE

MARCH 5. Cooley-Dickinson Hospital, Northampton.

MAY 7. Annual Meeting. Jones Library, Amherst.

NORFOLK

JANUARY 22. Veterans Administration Hospital, West Roxbury.

FEBRUARY 26. Boston Medical Library.

MARCH 25. Boston Medical Library.

APRIL 22. Boston Medical Library.

MAY 7. Place to be announced.

SUFFOLK

JANUARY 23. Massachusetts General Hospital.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 17

THURSDAY, JANUARY 17

*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.

*4:00–5:00 p.m. Medical Division Lectures. Mount Auburn Hospital, Cambridge.

5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Amphitheatre, New England Deaconess Hospital.

*5:00–6:00 p.m. X-Ray Conference. Mount Auburn Hospital, Cambridge.

FRIDAY, JANUARY 18

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street.

(Notices concluded on page xv)